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**ETHICAL ASPECTS OF THE NEWBORN SCREENING PROGRAM:
THE ISRAELI PROGRAM AS A TEST CASE.**

**ASPETTI ETICI DEL PROGRAMMA DI SCREENING NEONATALE:
IL PROGRAMMA ISRAELIANO.**

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Abstract

Background: In the past twenty years most western countries have been expanding their newborn screening (NBS) services, relying on novel bio- and information technologies. This process has been accompanied by significant lay, ethical and legal debates regarding the structuring of the expanded program and the roles it grants to personal parental choices and values. In order to better understand expanded NBS as a health service, this research focuses on the recently expanded Israeli program and examines it from different perspectives, especially ethics, public participation and cultural awareness in pediatric public health services and programs.

Methods: This research employs three main methodologies. Historical research of primary and secondary sources; bioethical analysis in the style of analytic philosophy; qualitative methodology in the form of in depth interviews with two groups of people (the Israeli National Newborn Screening Lab and certified home birth midwives).

Results: Whereas it is customary to represent NBS as a discrete and cheap universal public health service that prevents catastrophic inborn diseases, this thesis highlights NBS as a complex practice, which have impacted the contemporary construction of childbirth as a hospital based event, and that it has been constructed as a hybrid of public health and clinical service. Despite the explicit commitment to patient autonomy and parental responsibility, the framing of choice in NBS is not in line with the standards of respect for patients' autonomy in other areas of medicine.

The analysis of the Israeli program, data and policy exposes inconsistencies and ambiguities at the normative level as well as in the actual daily practice. This is borne out by the diverse avenues of information and communication strategies adopted. The professionals responsible for the screening program articulate commitment to universal coverage and diagnostic precision; home-birth midwives, who self-represent as an alternative to the mainstream biomedical

establishment, direct their critical attention to the notion of natural birth, practically relegating newborn screening to the spheres of pathology and expert opinion. Based on the research's findings and the literature on public participation in public services, the thesis concludes with a model for integrating public participation with expert authority in the planning of a health service such as the newborn screening.

Riassunto

Background. In questi ultimi vent'anni, molti paesi occidentali hanno espanso il loro programma di screening neonatale, grazie alle possibilità offerte dalle nuove tecnologie a disposizione. Tale processo di ampliamento è stato accompagnato da un significativo dibattito pubblico sugli aspetti etici e legali riguardanti le modalità attraverso le quali tale ampliamento viene realizzato e sul ruolo che in esso assumono le scelte dei genitori. Con l'obiettivo di comprendere più a fondo lo screening neonatale in quanto servizio di salute, questa ricerca si focalizza sul programma di screening neonatale recentemente esteso in Israele, esaminandolo da diverse prospettive, con particolare attenzione a quella etica e alle sue implicazioni a livello di partecipazione pubblica nei programmi di salute pediatrica.

Metodo. La presente ricerca utilizza tre metodologie. La ricerca storica di fonti primarie e secondarie; l'analisi bioetica dei principi che fondano lo screening neonatale; la metodologia qualitativa nell'analisi di interviste in profondità realizzate a due gruppi di persone: il team che lavora nel centro nazionale israeliano di screening neonatale e un gruppo di ostetriche che realizzano parti domiciliari.

Risultati. Mentre si è soliti rappresentare lo screening neonatale come un servizio pubblico universale, indipendente e relativamente poco costoso, che permette di prevenire lo sviluppo di malattie innate dagli effetti devastanti, questa tesi mette in evidenza lo screening neonatale in quanto pratica complessa, che ha avuto un impatto importante nella costruzione contemporanea dell'evento "nascita", inteso come servizio ospedaliero, e che attualmente si articola come servizio di salute a cavallo tra la salute pubblica e la medicina clinica. A livello bioetico, nonostante l'esplicito impegno nei confronti dell'autonomia del paziente e della responsabilità parentale nelle scelte di salute relative al proprio figlio, la formulazione delle possibilità di scelta

sembrano essere piuttosto distanti dagli standard di rispetto per l'autonomia dei pazienti presenti in altre aree della medicina.

L'analisi del programma israeliano, in particolare, mette in luce incoerenze ed ambiguità, sia a livello normativo sia a livello di pratica quotidiana. Questo emerge dalle diverse strategie di informazione e comunicazione intraprese. I professionisti responsabili per il programma di screening neonatale esprimono il loro impegno nei confronti del raggiungimento di copertura universale e della precisione diagnostica; le ostetriche domiciliari, che percepiscono il loro lavoro come alternativo all'approccio biomedico, focalizzano la loro attenzione esclusivamente sul concetto di parto naturale, considerando lo screening neonatale come appartenente alla sfera patologica propria di personale specializzato. Sulla base di questi risultati e della letteratura sulla partecipazione pubblica nei servizi alla popolazione, la tesi conclude delineando un modello che mira ad integrare partecipazione pubblica e professionisti sanitari nella pianificazione di un servizio di salute come lo screening neonatale.

CHAPTER ONE: INTRODUCTION

This thesis is dedicated to the programming of newborn screening (NBS), especially in its “expanded form”, in the era of information technologies (IT) and public participation in healthcare planning. More specifically, the thesis focuses on the ethical aspects involved in planning, using Israel as a test case.

In the 1960s, a practice of testing every newborn baby to a rare metabolic disease (phenylketonuria) began. It was the first time ever that a biochemical blood test allowed the pre-symptomatic diagnosis and the consequent prevention of a severe disease. In the 1970s babies were subjected to screening to hypothyroidism as well. Attempts to expand NBS further were stymied by lack of appropriate technology. But in the 1990s the electrospray tandem mass spectrometry technology (MS/MS) appeared, allowing the simultaneous testing of a small blood sample for many biochemical markers, and for a relatively very low price per tested item. With powerful computer technologies, the art of NBS has been revolutionized. But many new questions had to be addressed: which conditions should be screened? How to handle the huge amounts of blood samples and medical information? How to conduct research? and the like. The key questions behind all others were these: who should decide such things, and how?

Already in the 1970s, when bioethics and bio-law were emergent disciplines, regulators have incorporated ethical considerations and public participation in NBS programming. However, until this very day there is a marked variety among national – and sometimes even regional – NBS programs. Both in the USA and EU, the healthcare professionals who are responsible for NBS consider this lack of uniformity a serious challenge that need be addressed in the near future.

This thesis aims to contribute to this discourse by combining a broad spectrum exploration of the professional and ethical literature on expanded NBS with an in depth analysis of the NBS program in Israel. Israel was one of the first countries in the world to introduce NBS; but it adopted the MS/MS technology and expanded the program relatively late, in 2007, and after a small group of public health and genetics professionals studied the international experience of expansion. A few acts of secondary legislation govern NBS, and a primary law incorporating NBS in the Genetic Information Act (2000) is now under deliberation in the parliament. With a population of 8 million people, marked cultural diversity, advanced medical services and a national NBS program, Israel is a good test case for reflection on NBS programming in small European nations or big Italian provinces such as the Veneto.

Three methodological instruments have been chosen. The first is the application of conceptual instruments taken from the literature on democratic governance and programming of large scale healthcare services. The second is qualitative research in the form of interviews with specifically selected actors – mainly the people who are responsible for the national Israeli NBS program and a sample of midwives who, owing to the particularities of Israeli law, play a unique role in the administration of the clinical aspects of NBS. Third, analytical and critical methods from bioethics and bio-law are applied to the relatively large and comprehensive body of Israeli publications in terms of law, practice guidelines and official communications with the public.

Overall, the reader will find in this thesis two sets of insights. The first is local, pertaining to the particular circumstances of Israeli culture, legal framework and the structuring of its universal healthcare coverage. The second set of insights pertains to a principled understanding of the NBS as a meeting point of public health and clinical service. For example, the apparently

purely bureaucratic decision to finance NBS as a public health rather than a clinical service has been found to bear a few ramifications on the construction of public participation and patients' choice within the program.

The second chapter of the thesis is dedicated to the history of NBS world-wide. So far no comprehensive history of NBS has been written and the few articles published do not try to couch NBS within a broader setting of the history of medicine and medical ethics and law at the time. Because a working hypothesis of this thesis is that a proper historical perspective is crucial for the understanding of medical services, history, especially the social history of NBS, has been given a special emphasis at the opening of the project. The history is based on primary as well as secondary sources and on sources of oral histories available on the web.

The third chapter is dedicated to an in depth explication of the ethical problems found in the discourse on NBS. Rather than focusing on one regulative issue (e.g. exclusion and inclusion criteria) the thesis offers a systematic and comprehensive evaluation, aiming to expose the ways in which the diverse normative aspects of NBS reflect on each other.

The fourth chapter presents the Israel NBS program – its history, structure, regulation, cultural context, as well as the relevant data, mainly the most up-to-date statistics coming from the National NBS Center in Tel HaShomer Hospital. The chapter will also offer the first panoramic analysis of all legal documents that address NBS in Israel. As far as we know, it is the first panoramic analysis of all binding regulations addressing NBS anywhere in the world.

The fifth chapter explores the realities of NBS in Israel. This was possible through in depth interviews with the team at the central NBS service, as well as with a representative sample of homebirth midwives. One of the most intriguing discoveries of this research was the association between home-birth (1% of all Israeli births) and NBS. This fascinating fact is a

product of Israeli law which places unprecedented and unparalleled responsibilities of home-birth midwives in relation to NBS. We hypothesize that because women who choose to give birth at home are highly aware of both treatment options and their power to choose for themselves, a clustering of personal choices (or at least opinions) on NBS may be found within this particular population.

The last chapter draws on conceptual models that have been developed in the study and administration of large scale public services, especially in welfare and health care. We will examine how ideas such as “the citizen participation ladder” and “personalization” of services might shed light on the analysis of the problems and findings discussed so far. On this basis we draft a scheme for public participation in deliberation, programming and governance of NBS programs in ways that render ethical and other value-laden considerations (e.g. culture) bite deeply and effectively into the genuine concerns of the public, the health needs and values of patients and the overall framework of professional medicine in the era of bioethics, human dignity and democratic societies.

CHAPTER TWO: THE HISTORY OF NEWBORN SCREENING

The idea of screening

In 1951, the United States Commission on Chronic Illness defined screening as

The presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment’’.
(Commission on Chronic Illness 1957, 57).

This definition matured following decades of growing state involvement in public health and scientific understanding of large scale epidemiology. Significant turning points were the infant hygiene movement, of the late 19th century, and the medical exams involved in the conscription of millions, during the World Wars (Starr 1982, 192-195). For example, the army was highly motivated to detect draftees with rheumatic heart lesions that might develop into clinically significant heart disease in the conditions of physical training. The doctors involved in the screening of candidates to service realized the public health value of timely detection of so-called silent conditions. With the success of other major public health campaigns, hopes were generated that therapy, not only avoidance of harmful stressors, might become feasible upon systematic, large-scale and coordinated efforts towards early detection.

The full justification of screening is that early and fast detection of the disease will allow timely and effective medical response, which will significantly reduce hard endpoints of the natural history of the disease, such as disability and mortality.

The very same idea of screening is revolutionary in its own right, because it breaks ground with the traditional paradigm of cure, where illness is seen as a private event to be cared for within the clinical encounter. In the classical form of doctor-patient relationship, a doctor takes care of a patient that has previously contacted him because of symptoms that may indicate a pathological situation. In the past, many people, especially the affluent, consulted doctors for personalized advice regarding health promotion and prevention. But universal and impersonal public interventions, such as vaccination and screening, were not in practice. Only with the new paradigm of screening, doctors started approaching potential patients with regard to the possibility of asymptomatic – hence "silent" – but smoldering fatal conditions that might be specifically tested, even when the tested person feels absolutely well and show no signs of sickness.

Screening is peculiar for one more reason. Although it is an intervention of public health, because of state involvement, it cannot be characterized as preventive in the full sense of the word, such as vaccination, since it is not about prevention of sickness, but about alteration of the natural history of a pathology that has already set in.

Programs of screening usually focus on a circumscribed population defined by specific epidemiological characteristics (such as age, sex, or occupation). Proper selection of the population to screen is necessary for obtaining the needed levels of accuracy.

With the establishment of the United Nations (1945) and the Universal Declaration of Human Rights (1948), a new sensibility of global responsibility to better the health condition of humanity emerged. The healthcare arm of the UN, the World Health Organization, commissioned James Maxwell Glover Wilson, the Principal Medical Officer at the Ministry of Health in London, England, and Gunner Jungner, the Chief of the Clinical Chemistry

Department of Sahlgren's Hospital in Gothenburg, Sweden, to write a Report on screening. Their work was published in 1968, under the title "Principle and practice of screening for disease", and it became a classic in public health on screening until today. In it, the authors affirm that "the object of screening for disease is to discover those among the apparently well who are in fact suffering from disease". In this sense, "...screening is an admirable method of combating diseases, since it should help detect it in its early stages and enable it to be treated adequately..." (Wilson and Jungner 1968,7). The Wilson and Jungner's report has had a lasting influence, as it is cited as a fundamental reference by the medical, ethical and legal literature on the expansion of NBS. This is very interesting, especially in the light of the following words that the authors write in their introduction,

We have not, for instance, included the practice of early disease detection in the maternity or child welfare field, largely because that practice is so well established. (Ibid. 9)

This is an extraordinary remark since, at the time of their writing, most countries did not perform NBS, the few who did tested only for PKU, and fetal ultrasound was not yet born. Whereas one might expect the authors to focus precisely on the nascent technologies of prenatal and postnatal screening, it seems that they have taken them for granted, focusing instead on chronic illnesses typically present in developed countries, such as pulmonary tuberculosis, visual defects (including chronic glaucoma), hearing defects, syphilis, diabetes, cancers of the skin, mouth, breast, cervix and rectum, hypertensive disease and ischemic heart disease (Wilson and Jungner 1968, 17). What were the reasons of their explicit decision to exclude NBS? It is difficult to answer. Perhaps the authors did not want to address a topic that might implicate sensitive issues, such as abortion and eugenics. Perhaps they had seen NBS already developing

following concepts somehow different from what they considered screening to be. An example of this is the importance that the authors give to the definition of the population at risk to which offering screening, by careful statistical calculations. As we will see later on, when screening for PKU began, a proposal to focus on children at risk only (e.g. family history) was immediately rejected, because the test to perform was considered very simple and very cheap, newborns were easily available (being already in the hospital) and the initiators of the program also adhered to a newly formed mission of “not to miss a single child”, which clearly rejects any statistical evaluation. Wilson and Jungner do not offer arguments supporting the universalization of screening programs either. At the contrary, universalization stands in opposition to the paradigm of scientifically informed screening, which seeks to focus on the relevant population, knowing in advance that some patients will be left out. For example, screening for breast cancer begins at age fifty, even though a fraction of patients might benefit from early detection at an earlier age. Rather, the very rarity of breast cancer below the age of fifty is the reason why women at this age group are excluded from screening. This policy is not interpreted (at least by policy makers) as lack of concern to the health of young women, but as a measure of cost-effectiveness and benefit-harm balance of screening tests. Besides, in comparison to the diseases discussed by Wilson and Jungner, NBS targeted a much rarer condition. While the prevalence of diabetes is 5%, for example, and the incidence of cervix cancer is around 1%, PKU is hundreds of times less common (0.01%).

Anyhow, whatever the reasons for excluding NBS from their report, Wilson and Jungner’s work became a de-facto reference for all NBS literature, especially in relation to the screening criteria needed in order to develop – and eventually expand – a screening program. NBS became such a central topic that the very same revision of the “Wilson and Jungner

criteria” done by the WHO forty years after their publication refers almost exclusively to it (Andermann et al. 2008)

Wilson and Jungner document has been very influential, especially cited in relation to the ten criteria or "principles" of inclusion they formulated (Wilson and Jungner 1968, 26-27).

Wilson and Jungner’s criteria for screening
1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

In the publication of the WHO, written on the occasion of the fortieth anniversary of the Wilson and Jungner's report, it is presented a literature review on the principles for screening, from 1968 to 2008, under the title “Synthesis of emerging screening criteria proposed over the past 40 years” (Anderman et al. 2008).

Synthesis of emerging screening criteria proposed over the past 40 years (from Anderman et al. 2008, 318)
<ul style="list-style-type: none"> • The screening program should respond to a recognized need.
<ul style="list-style-type: none"> • The objectives of screening should be defined at the outset.
<ul style="list-style-type: none"> • There should be a defined target population.
<ul style="list-style-type: none"> • There should be scientific evidence of screening program effectiveness.
<ul style="list-style-type: none"> • The program should integrate education, testing, clinical services and program management.
<ul style="list-style-type: none"> • There should be quality assurance, with mechanisms to minimize potential risks of screening.
<ul style="list-style-type: none"> • The program should ensure informed choice, confidentiality and respect for autonomy.
<ul style="list-style-type: none"> • The program should promote equity and access to screening for the entire target population.
<ul style="list-style-type: none"> • Program evaluation should be planned from the outset.
<ul style="list-style-type: none"> • The overall benefits of screening should outweigh the harm

This synthesis of emerging criteria fulfills Wilson and Jungner’s original wish that discussion and revision of their work follow,

If anywhere we have appeared dogmatic, we hope this may serve to stimulate discussion, since, in the end, real development depends on an exchange of views. (Wilson and Jungner 1968, 9).

Whereas one may gather ethical concerns in Wilson and Jungner's criteria under the maxim of "acceptability to the public", the 2008 list (which does not intend to replace Wilson and Jungner's but to show how they have been integrated and expanded by others) dedicates more attention to ethical concerns, mainly respect for autonomy and to equity.

In order to better understand the maturation of the contemporary governance of NBS, we now turn to inquire the historical roots of screening and the special role "genetics" has come to play in it.

The seeds of New Born Screening (NBS)

It is well known that the history of newborn screening is interwoven with the history of phenylketonuria (PKU) and with the discovery by Dr. Robert Guthrie and his assistant Ada Susy of a simple method of testing the levels of phenylalanine in the blood (Guthrie and Susy 1963). But to reconstruct the conceptual map that preceded this discovery and that supported the whole creation of newborn screening may allow us to rebuild the epistemology of screening and to shed some light on some key elements still present in the actual debate on screening.

Some events paved the way to the discovery of the Guthrie test.¹ The first one is the development of the concept of "inborn error of metabolism", which was first used by Sir Archibald E. Garrod, during a lecture delivered before the Royal College of Physicians on June 1908 (Garrod 1908).

¹ See the series of lectures on the history of newborn screening, by Dr. Harvey Levy, from the Children's Hospital Boston Intellectual and Development Disabilities Research Center (IDDRC) at http://www.mrrcmedia.org/flashcast/nbs_home.html

We should naturally expect that among such abnormalities those would earliest attract attention which advertise their presence in some conspicuous way, either by some strikingly unusual appearance of surface which responds to a test habitually applied in the routine of clinical work, or by giving rise to the obvious morbid symptoms. Each of the known inborn errors of metabolism manifests itself in one or other of these ways, and this suggests that others, equally rare, which do not so advertise their presence, may well have escaped notice until now (Garrod 1908, 3).

In this seminal text we can trace some of the technical and ethical issues that will later develop in the discourse of newborn screening. Until this time, doctors would talk about "disease" or "deformity" as something that was evidently pathological and therefore should be treated, as much as our ability and knowledge would make it possible. But Garrod's approach suggested a novel concept in order to describe alterations that are not mere variants of ordinary chemical pathways, but cannot be directly and univocally linked to a pathology either. For this reason, he could not fit this negative property within the binary structure of health/disease. Hence, he availed himself of a different metaphor, referring to his findings as "errors". Mathematical and other kinds of errors may be logically incorrect, but they do not necessarily cause "harm". Whatever the reason for this terminological choice, what is relevant to our analysis in Garrod's scheme is that a metabolic error does not necessarily entail a disease. Sir Garrod himself underlines this insight, by writing,

Some of them produce no obvious effects which compel attention, and may only be accidentally detected in adult life, and neither the evidence of the patient himself nor that of his parents can be of any help in endeavoring to trace back the peculiarity to infancy. (Ibid. 3)

The error that Sr. Garrod referred to is the inability to convert some metabolites into other metabolites within the human body. This abnormality seems to be rare. When no obvious morbid symptoms appear, it can only be discovered by noticing some unusual appearance of tissues or excreta, or even accidentally. Most probably, some people are born with this altered metabolic pathway.

Theoretically any anomaly which claims a place in the group should be present from birth and should persist throughout life... (Ibid.3)

Although at the time Mendelian laws of heredity were already well known, it was unclear when the error should appear, since not all chemical abnormalities could be traced to genetic dominant/recessive transmissions.

When referring to a test as a method to detect the defective metabolic pathway, Garrod does it within a clinical perspective. Testing was necessary in order to help clinical work. Discovery of these “errors” was a side effect of diagnostic testing of already known signs or symptoms. Some of these “errors” might have present or future clinical significance; but many might not. Garrod was not sure whether it was possible to harbor a “metabolic error” for life and remain disease free. However, he pointed out that finding an “error” is different from diagnosing a clinically relevant condition; and that some people might suffer from an “error” without anybody realizing they have a disease.

Only the creation of a test specifically designed for the purpose of finding a metabolic error would allow the screening idea to come to reality, turning testing as an efficient method to fishing out future patients. But the potential burden on tested but healthy people, as well as on society, was not been contemplated about.

From our analysis of Garrod's text, we can draw a few insights that are significant to the actual debate on newborn screening. The first one is that a meaningful difference exists between "error" and "disease". The meanings of these two words do not overlap; they are not synonymous. Mistakes found in the biochemical processes of a human body may have different impact on the actual health of the individual, which varies from severe illness to no adverse impact. Therefore, logically speaking two consequences apply. The first one is that identification of a metabolic variation does not necessary entails the identification of a potential patient. The second insight is that in order to define a person as a patient we need at least two elements: 1. the isolation of the pathological impact of the "error" on the health of a specific person and 2. the engagement of this person in a therapeutic relationship.

These last considerations bring us to evidence a third relevant point that emerges from Sr. Garrod's analysis and that is a central aspect of the discussion on NBS today – the “clinical perspective” of testing. In fact, the existence of an appropriate test is relevant as long as testing itself would allow prompt and effective intervention, directly linking diagnosis with therapy. No presumption was made about testing without a relevant therapeutic impact.

The clinical relevance of diagnostic tests was also the main motivations that lead to the discovery of the Guthrie test. In fact, Dr. Guthrie's initial efforts were directed to find a way to evaluate the levels of phenylalanine in the blood of patients already under a specific diet low in phenylalanine; only later, once it had been proved that the efficacy of the diet would increase in relation to the time of its initiation, such a test was adopted in order to find increased levels of phenylalanine even before diagnosis has been made. It is difficult to overstate the paradigm shift involved. Initially, “diagnosis” was always a clinical one, while the biochemical tests helped in doubtful cases and in the classification and follow-up of patients. Confidence in the biochemical

assays and attempts at earlier and more effective therapeutic interventions brought forth the notion of laboratory-based diagnosis that is independent of any clinical manifestations. Indeed, public health officials explicitly warn against the establishment of diagnosis solely on the basis of screening tests; but in actuality, a positive test sets off a diagnostic alarm until proven otherwise.

Because “errors of metabolism” were classified as “inborn”, it was possible to think about diagnosing future illness almost immediately after birth by means of detection of “errors” that are linked to future diseases. In the new era of hospital-based child-birth, perinatal care was a convenient and efficient context for massive testing.

Since clinical reliability of even the most scientifically precise tests depends on the prevalence of the tested condition in the population (the pre-test probability), a positive test result does not “diagnose” metabolic errors, but creates “suspicions” that merit further, repeated or more specific tests. Lab-based diagnosis has become twice removed from clinical manifestation of disease. First, the test aims to capture a condition even before it is clinically manifested; then, a positive test has the power to raise suspicion, but not to diagnose a disease.

One more complication developed from positive tests results, when their clinical significance is unclear even after they have been properly verified. In this way, Garrod’s distinction of “error” and “disease” resurfaced in a new form, especially within expanded newborn screening programs, since for certain conditions, the information obtained does not have necessarily a clear clinical significance. One examples is hyperphenylalaninemia, when elevated (relative to average “normal”) phenylalanine is detected, but still below the pathological levels associated with PKU. In Israel and other places, these children are sent for follow up in the PKU clinic, without any significant pathology found so far.

But while this “unclear clinical information” or “error without disease” may be criticized from a “clinical perspective”, it becomes more at ease when approached from a “preventive perspective”, where concepts such as “non-disease” or “pre-disease” fit better the paradigm of prevention.

The second event that led to newborn screening is the discovery of PKU in 1934, which basically proved the theory of inborn metabolism disease. In the case of PKU, urine responds to chlorine test by changing its color. Normally, phenylalanine is converted to tyrosine by the enzyme PAH, but in PKU this enzyme is defective therefore disrupting the normal pathway of the metabolites. This is why in PKU the phenylalanine that is not converted to tyrosine accumulates in the urine in high quantities and produces the hyper phenylalanine. PKU was a clear cut case of an “inborn error” that leads to a devastating disease.

In 1953, a German doctor, Horst Bickel (1918-2000), fellow in training at the Children's hospital, Birmingham England, showed that, by following a specific diet, retardation would partially regress and the child would show clear signs of improvement. The dietary intervention worked like a switch that corrects an error. In a landmark movie, Bickel shows one of his first patients, a two year old toddler named Sheila as her behavior improves and deteriorates upon the introduction and withdrawal of the diet.² This extraordinary achievement inspired clinicians and researchers to find a test that might help diagnose babies as early as possible. In the late 1950s different methods to test phenylketonuria in the urine were developed and applied to specific groups, such as patient in a mental institutions, children with mental retardation, or outpatient clinics, in order to find out the incidence of cases, to check the reliability of different tests, to

² There were only 3 copies of the movie, now available at <http://www.youtube.com/watch?v=-rs0iZW0Lb0>

determine the ideal window time in which to perform them or the format that would increase participation in testing, as well as to inquire about the impact of the diet on IQ, among other aspects (Centerwall et al. 1960).

Because it was quite difficult to follow Bickel's diet, it was not clear whether unsatisfactory response resulted from late institution of therapy or lack of adherence. A search for an assay that would monitor the presence of active disease (the manifestation of the "inborn error") was undertaken by Robert Guthrie, a microbiologist from Buffalo, New York. Guthrie had a son with undiagnosed type of mental retardation and a nephew who was diagnosed with PKU at age two.

By studying more in detail the case of the nephew and getting involved with the National Association for Retarded Children (NARC), Dr. Guthrie came across an article³ that stated how mental retardation caused by PKU could be prevented with early introduction of the right diet (this case report referred to children who were found relatively early because of older siblings already affected by PKU). He decided to work for the cause, by transforming his bacterial assay, which would identify certain metabolites in the blood and urine of patients with cancer, into a test that could isolate metabolites whose blood levels rise in PKU patients (Guthrie 1996; Centerwall and Centerwall 2000).

Together with his assistant Ada Susi, Dr. Guthrie managed to create a simple and reliable test for the detection of elevated phenylalanine levels in the blood. The test was applicable on a dried spot of blood, thus eliminating the technical problems associated with fresh sampling, separation of plasma or serum and anticoagulation. Guthrie's method allows a nurse to prick a

³ Frederick A. H. and C. W. Streamer. 1959. Phenylketonuria treated from earliest infancy. Report from three cases. *American Journal Disability Child* 97:345-347.

baby, let a few drops of blood be sponged by a filter paper and then send the dried paper for lab analysis (Guthrie and Susi 1963).

In the 1940s and 1950s the diagnostic criteria and dietary measures were not yet mature, owing, mainly, to dependence on clinical diagnosis made on sick children. Guthrie's test was both simpler and more accurate, and its appearance coincided with consolidating knowledge on PKU and novel political and cultural sensibilities regarding the prevention and treatment of mental retardation. Guthrie's invention came shortly after the FDA approval in 1958 of the first commercial dietary formula for PKU. Although it was originally meant to assist in the follow up of already diagnosed children, the potential of this simple test for the screening of apparently healthy babies was evident from the beginning.

Even before his results were fully published in a scientific journal, NARC had campaigned for large scale newborn screening for PKU. Guthrie waived financial gains for his invention (Holt Koch 1997, 44) and NARC expected the public to pay the 50 cents cost of each test (Paul 1999; Paul 2008; Committee for the Study of Inborn Errors of Metabolism 1975, 24-28).

This episode encapsulates a landmark step in the interaction of medical technology and medicine as a social practice. For the first time it was possible to apply a scientific test to an apparently healthy newborn child and foretell an imminent but preventable catastrophic disease. Even though the disease is quite rare, affecting 1/15,000 in the USA, the combination of easy and reliable testing in terms of costs and administration (almost all Western children are born in hospitals) rendered it reasonable to expect the public to screen every newborn, investing 7,500 US dollars in the prevention of one case of life-long severe mental retardation. One might have suggested that tests be offered only to babies at risk (e.g. with family history), but NARC

committed itself to the ambitious goal of finding in time every affected baby. This ambition might have been bolstered by the early twentieth century successes at the eradication of cretinism, a very common form of retardation caused by lack of iodine in the diet of people living in poverty, away from the sea, which is the natural source of iodine. In 1924, an American salt company began to add iodine to its table salt and many other produces followed suit. This resulted in a marked reduction of cretinism, the most significant and successful public health intervention aimed at mental and developmental retardation (Merke 1984, 234-250; Feyrer, Politi and Weil 2010). It has been shown that large scale, universal and uniform intervention can significantly prevent childhood disease and disability. It is no accident that the second condition screened is congenital hypothyroidism.⁴

We may observe that the combination of cheap and friendly technology with the institutionalization of child-birth and growing state responsibility for public health and children's welfare allowed activists to break new horizons in terms of diagnostic testing and mass screening. The historical circumstances were friendly to such a move. In 1962, child abuse was medicalized as a distinct syndrome that physicians are responsible for not missing

In spite of the extraordinary results and the evident benefit expected of early diagnosis and treatment, the initial response of the scientific community was far from enthusiastic. Physicians as well as researchers expressed a spectrum of concerns. Some doctors were still skeptical about the ultimate benefit of the diet therapy for PKU. Others were more concerned

⁴ Cretinism is life-long deficiency in thyroid hormones mostly owing to iodine-poor diet; congenital hypothyroidism results from abnormal development of the thyroid gland and cannot be amended by supplemental iodine. If left untreated, it may develop into cretinism and even death.

with the possibility of bending medical care towards a more "socialized" practice, allowing more interference of the state. In fact, testing all newborn children indiscriminately needed the support of a specific federal legislation. Because public health was already the acknowledged responsibility of the public, from this perspective NBS was perceived as a clinical rather than public health service. Where this universalization of medical care and obligatory measures of public health would have lead medicine in the future? As a matter of fact, not only collecting blood spots were at stake, but also performing the test in a web of public laboratories, consequently jeopardizing the private market. Critics were also questioning the reliability of the Guthrie test, and many other unknown data of phenylalanine levels that might have led to possible overtreatment of mild cases, the management of false-positive results, and the whole idea of mandating screening for newborns (Paul 2008). Whereas the validity of the test and the therapeutic role of the diet were quite clear, no conclusive quantitative evidence was available with regard to the precise impact of mass NBS to PKU. The critics thought that technology needed to mature much more before it is applied to whole populations; advocates thought that responsibility for thousands of children compels immediate mass screening.

At the end, not only the results of the test and the clear benefit for the few children detected overcame the resistances expressed; but the whole legislative decision-making process was strongly influenced by the direct intervention of patients' associations, political sensibility and the press. A progressive extension of the screening program spilled over from Massachusetts to all other federal states. By 1967, thirty seven states had PKU laws, and by the mid 70's, every state had done so, mainly without significant opposition. Most of these laws render NBS compulsory.

For two reasons the advent of newborn screening to PKU marked a conceptual revolution in the history of medicine. For the first time a universal public health program was targeted at a rare condition, and, second, it became mandatory in many states, even though it involved neither contagion nor other threats to the public.⁵ A third groundbreaking factor was the leadership of advocacy groups in the establishment of a public health program. Patient and public advocacy groups were a new phenomenon, of which NARC was among the first. While the professionals expressed caution with a new technology, the public pushed policy making ahead towards the formation of a universal, publicly subsidized, mandatory service (Paul 2008, Ross 2011).

The NBS service could have taken different tracks. Nothing in the nature of the service precluded a universal and hospital based coverage. Indeed, in 1958, kits of urine tests for PKU were sent to all women who had given birth in Cardiff. The kit was accompanied with instructions for self-performance of the test. Those tested positive (change of color), were instructed to bring the child to medical care. Compliance rate was over seventy percent; but many mothers had difficulties with the performance of the test (Gibbs and Wolf 1959). At the same time, most health department districts in California ran a similar pilot study, employing a much easier test – the diaper test. It was not necessary anymore to capture fresh urine, but it was possible to apply the test kit to wet diapers (Centerwall and Centerwall 1958). Abnormal levels of PKU appear in the urine only in the second week of life; hence, some have suggested the idea of attaching screening to the first session of vaccination (Centerwall et al. 1960).

The mass transition to hospital birth and lost opportunities for home birth (in the USA) rendered this mode of thinking obsolete. Once childbirth is medicalized, it is reasonable to instill

⁵ Since the late nineteenth century, circumcision had already been almost universally practiced on American neonates as a public health measure of “cleanliness” (Gollaher 2000, 73-92).

the screening of every baby, even the “least suspicious” ones. Rather, since then the public has grown to regard every baby as potentially sick until proven otherwise.

In 1960, the reduced medicalization of screening was considered helpful in its universalization:

To place the mechanics of testing into the hands of the parents so that even the least suspicious patient is tested. (Allen 1960).

Two factors may account for this approach. The first is the unprecedented success of universal enrichment of table salt with iodine. But we have not found explicit evidence linking the eradication of cretinism to NBS. The second is economic considerations – the calculated cost-effectiveness of preventing life-long hospitalization (Centerwall et al. 1960). This consideration is explicit. But the calculation unclear. With the estimate of 200 PKU babies born annually in the USA, early detection of all would save \$20,000,000. But since 68% of PKU cases already have a known sick relative, the costs of universal screening should justify only 30% of the estimated sum of \$20,000,000.

Deployment of the Guthrie test during the first vaccination session or pediatric visit has never been entertained. Despite the fact that 70% of new PKU cases had a known familial occurrence, rarely screening for “babies at risk” (with a family story of retardation or PKU), leaving others untested was not carried out either. Against the ordinary logic of screening that seeks a target population at risk, even before Guthrie’s invention, public health officials sought to screen even “the least suspicious patients”. These babies were “patients” even though they were “least suspicious”.

Since the beginning of screening, scientists were wondering about the possibility of searching for other pathologies with characteristics similar to PKU. The pathologies that they

had in mind were called "inborn errors of metabolism". In particular, they were thinking about conditions with the following characteristics - a) diseases that were considered severe, b) diseases that could be detected early (or in a pre-symptomatic stage), and c) diseases for which an effective treatment already existed, significantly reducing bad outcomes of the disease (mental retardation or even death).

All of the above characteristics were fitting the Wilson and Jungner's criteria. Because most of the affected patients do not have sick relatives, scientists had especially in mind autosomal recessive disorders. Initially, they explored metabolic defects such as maple syrup urine disease (MSUD) and homocistinuria (or CBS deficiency), but a technical problem that "acted as a significant brake on test proliferation" was that adding a new disease meant to create an independent test, thus increasing the amount of blood collected from each child and the added costs of lab analysis (Paul 2008, 11). Only in 1973, after a research team from Canada announced that they could detect congenital hypothyroidism (CH)⁶ by carrying out a radio-immune assay on the Guthrie card, the door to expansion started opening. The expansion of NBS did not increase the burden on the baby, however miniscule, but managed to derive new benefits from the old and trusted Guthrie card.

In the 1990s, the development and the application of the electro-spray tandem mass spectrometry (MS/MS) to NBS allowed the testing of numerous metabolites using only a few

⁶ Congenital Hypothyroidism was an already well known pathology, three times more frequent than PKU, that is characterized by a defect in the production of the thyroid hormone. If not treated, this deficiency can produce multiplex damages all over the organism, especially to the nervous central system, with important mental retardation. All this could be avoided by early and constant hormone therapy.

drops of dried blood (Millington et al. 1990). MS/MS effectively screens for amino acid chains, so that a single sample can be tested for multiple disorders. This great technical achievement permitted the testing of babies for more diseases without increasing medical and technical interventions, such as collecting more blood from the same child. It also allowed the unification and uniformization of techniques previously used - such as the bacterial inhibition assay used for the Guthrie's card (BIA). This new technology is very costly, but once available, screening programs were left "only" with the decision of what diseases to include in their analysis. This decision was soon to be proven not easy. In one significant way, the expansion of NBS has not altered one aspect of the first NBS program – both in the 1960s and in the most ambitious screening programs of the 21st century, the baby suffers the very same prick, and the blood spots are sponged on the very same paper card. This aspect of screening made the expanded NBS appear as identical to the well-established PKU testing.

In fact, at a first glance, the application of the technology seemed a logical solution in order to overcome those technical limitations previously experienced. Yet, the removal of the hurdle of “one sample – one/two test limit” cleared the way to a complex panorama, in which new problems progressively took form. As a matter of fact, unlike conditions previously added, which were generally highly penetrant, associated with high morbidity and mortality, and which early detection was an essential part of the successful instauration of a treatment, MS/MS can identify abnormal metabolites that may or may not be associated with serious morbidity and mortality, that may or may not have serious clinical symptoms, and may or may not have effective treatment available (Paul 2008).

By the late 2000s, most industrialized countries have expanded their NBS programs. It has never become clear whether MS/MS merely allowed public medicine to overcome the

technical and financial barriers on the way to the detection of additional conditions like PKU, or whether the availability of expansion made it desirable to screen for conditions that fall at the margins of the standard criteria, but, nevertheless, bode some benefit to the child. While genetic testing is already employed in the verification of positive screening results, the transition to mass population screening by means of DNA analysis seems imminent. It will allow direct access to genetic data and the testing of thousands of genetic markers in a single swath (Dhanda and Reily 2003; Goldberg and Sharp 2012).

One of Wilson and Jungner's criteria for screening is "acceptability to the population" of the screening and relevant treatment (Wilson and Jungner 1968, 31). Many people, clinicians and ethicists have come to question the circumstances in which expanded, let alone genomic, mass newborn screening might be "acceptable" to the public, if at all. This is especially relevant in the light of the observations that NBS is mandatory in many places, that the awareness of parents about the expanded program and its significance is unknown, and that "most screened conditions are not only rare, but also do not fit with common concepts of disease and illness. In general, elaborate preventive protocols have to be followed by patients who have never had or will have any symptom" (Burgard et al. 2012, 620; Timmerman and Buchbinder 2010).

For these and other reasons, the expansion of NBS due to the application of MS/MS has been criticized as "technological determinism" (or, "technological imperative"), where the mere existence of a new technology becomes the very same reason why it is used.

In this chapter we have reviewed the history of NBS as a convergence of diverse lines of scientific progress, social trends and technological development. On the scientific tract, the notion of inborn and life-long "errors" that might bring forth treatable diseases broke the horizons for very early pre-clinical diagnosis of a stable trait attached to a future and preventable

condition. The traditional dyad “healthy” v. “sick” was replaced by a triad “healthy”, “sick” and “healthy with an inborn error with possible future clinical significance”. With the growth of public health and state responsibility for mental retardation, this “possible future clinical significance” was translated to “clinical significance” in the sense that every child should be medically tested. The shift of childbirth from home to hospital, and from the private sphere to publicly supervised and uniform settings invited the creation of a standard test that is now part of childbirth, and not necessarily an individually tailored exam order by a pediatrician owing to early symptoms or familiar history. The development of reliable and highly effective treatment for PKU and hypothyroidism, together with the availability of cheap, accessible and reliable technologies for screening, rendered NBS a universal and uncontested practice. Treatment for some other and much rarer conditions were of much less clinical benefit, and the even cheaper possibility to test for almost endless number of metabolites and “errors” might have opened the way to a utopia of universal early detection and child health; but it also parted ways with the wall to wall consensus about screening. The rarer the conditions, the heavier the burden on the healthy and society; the less we know about the tests, the more diversity we find in NBS programs and policies. More than a hundred years ago, Garrod asked his audience whether every “error” is linked to a disease; today, many scientists are not confident whether tested “errors” are actually “errors” at all and whether early knowledge is always beneficial.

CHAPTER THREE: THE ETHICAL ISSUES WITH NBS

Introduction

Normative and ethical issues have always been part of the practice of medicine. The contemporary discipline and paradigm known as "bioethics" emerged in the last fifty years within specific socio-historical contexts.

The first time that the word "bioethics" appeared was in 1971, when Van Rensselaer Potter, a biologist and biochemist, wrote a book called "Bioethics: bridge to the future". The meaning of bioethics, at its beginning, referred to a comprehensive and global approach to the equilibrium of life over earth and its sustainability. This global and ecological perspective soon expanded to encompass a more specific understanding of bioethics, as the area in which ethical analysis of moral issues are raised by modern medicine and bio-science. For a few decades the public had been alerted to the risks inherent in modern medicine and to the fact that benevolence (i.e. good intentions) does not always produce beneficence (i.e. the good of the person and humanity overall). While it seemed relatively easy to curb the risks of maleficent medicine (e.g. the Nazi experiments), recognition of the dangers involved with good medical practice could be quite challenging.

There are at least three social factors behind the advent and maturation of bioethics - the process of emancipation of patients, the development of new technologies, and the evolution of medicine into a complex economic, political and social organization. Let's analyze them briefly. Classical medical ethics was based on the idea that not only does disease alter the individual's physical equilibrium, but also the mental one, to the point that patients were considered unable to take personal decisions regarding their own health. Therefore, the doctor had the responsibility to instruct the patient and steer his or her conduct. For this reason, the primary virtue of the

classical patient was obedience. This kind of doctor-patient relationship is asymmetric and vertical, authoritative, quite similar to the one between father and child. This is why this kind of relationship is labeled "paternalistic". The physician assumes the role of the father in the pursuance of the best of the patient/child.

Only at the beginning of the 1970s, the relationship between doctor and patient embarked on a process of "horizontalization", where both parties were considered autonomous and responsible adults actively involved in the process of shared decision-making regarding health care. It is then when the first charter of "rights of patients" appeared (1972). The doctrine and practice of "informed consent" is emblematic of the transition of doctor-patient relationship from a private sphere of trust and authority to the regime of rights, and the empowerment of individuals relative to both professionals and bureaucratized public (or: publicly supervised) services. In the doctor-patient relationship, the physician has the scientific knowledge and the technical information about health and disease, but the patient has the capacity to understand the situation and to decide whether to consent or withhold consent to care. This may include choice among alternative therapeutic strategies as well as the power to refuse diagnostic tests and all other medical procedures. Indeed, in the prevailing legal and moral paradigm, every medical act takes place within a health care relationship based on trust, where the two parts deliberate how to structure the health care process. The patient chooses his or her doctor freely and then either consents or refuses consent to specific acts of care. When circumstances do not allow for the process of informed consent (e.g. emergency, loss of mental capacity), doctors must act upon consent-based courses of action, such as presumed consent, consent by a proxy and advanced directives.

In parallel to this social transformation of the relationships of care, the enormous progress of medical technology opened a new arena for a multitude of problems and ethical conflicts. From the 1960s on, technological breakthroughs such as dialysis and artificial ventilation facilitated the medicalization and technologization of the end life, and brought about the need of revisiting the concepts of death and dying. Among the new questions were, who should access these expensive and scarce resources? When is it possible to withdraw a respirator? Should we follow only medical criteria or also patient desires should be taken into account? Of no less significance was the increasing ability to control and manipulate the beginning of life, especially the areas of sexuality and reproduction, with the introduction of technologies such as genetic engineering, IVF and prenatal diagnosis. What are the ethical principles that should guide us in these areas? How can we define what is moral/immoral in a pluralistic society? Such questions called for a comprehensive and coherent approach that sought foundations both in moral theory (or theories) and public legitimization.

In addition to the impact of technology, the bureaucratization of modern medicine brought with it considerable moral and legal challenges as well. Clinical care shifted from the private domain of doctor and patient, moving into a huge and expensive collaborative effort encompassing various experts and their supporting team of professionals such as nurses, dieticians, physiotherapists, psychologists, and lab technicians as well as administrators, computer operators and the like. For the very first time in history, all citizens had the opportunity to access health care and the very definition of health became a theme of human rights.

The jargon of bioethics and its conceptual framework were born in reaction to the exposure of some medical scandals, mainly unethical experiments on vulnerable patients. President Gerald Ford was the first state leader to summon a national committee for the sake of

delineating ethical standards for the new era of biomedicine. The first report of the President's Commission on Bioethics was published in 1978 (The Belmont Report), and it shaped the bioethical landscape ever since. Because the USA was a pluralist state, the Report did not found medical ethics on particular moral doctrines or religious values, but on three universally held principles – beneficence, respect for autonomy and justice. The academic elaboration of the report incorporated a fourth one – non-maleficence. During the international diffusion of the "Four Principles", others were proposed as well, respect for human dignity, for example. However, the thrust of the new bioethical language does not lie in a canonized list of moral values, but in a non-doctrinaire approach to moral problems as conflicts among basic, universal, *prima facie* values.

The first new born screening programs appeared just before the “bioethics” revolution. It might be said that some of the characteristics of NBS are emblematic of the social circumstances from which bioethics sprang forth – scientific discoveries that fast metamorphose into technology that is applied on a large scale under the aegis of the state. The expansion of NBS, however, took place in the 1990s with full awareness of bioethical concerns. The key ethical questions were on the table right from the beginning, but the novel language, social processes and legal instruments for dealing with them, were available only for the expansion phase. It was then when the new technology of tandem mass spectrometry (MS/MS) and advances in genomics put forwards additional questions and sharpened worries.⁷

NBS is a special field for bioethical inquiry, since it combines two distinct domains of medical practice - public health and clinical medicine. As a public health program, NBS

⁷ Genomics is a general name for the use of sequencing and information technologies in applied contexts, such as medical research, data-banking and forensics.

responds to the logic of the common good through a preventive medical action that aims at finding sick people among a defined population (in our case, all newborn babies); in its capacity as clinical medicine, NBS affects directly every baby who tests positive. From that moment on, he or she becomes a "patient" "suffering" from the possibility of harboring a catastrophic condition. The baby must be subjected to definitive or repetitive diagnostic tests and evaluations until the final diagnosis is made. Even though most positively tested babies are found healthy (i.e. the test is found false positive), all of the tested babies, and their families, must pass through the healthcare system like any other patient. But they are a new kind of patients, not persons who seek cure or care, but persons who need confirmation that they are healthy.

The practice of NBS is even more complicated by the fact that it targets children. In this case, parents (or guardians) have the right and the responsibility to take decisions on behalf of their children, but this freedom, also related to the private sphere of the family, is not unlimited. When parental decisions go against the clear interest of the child, the agents of the state may interfere. Such interference stems from the medieval common law doctrine of *parens patriae*, according to which, the Crown (now, the state) bears the ultimate responsibility for the wellbeing of all incompetent subjects.

In the following section we survey and analyze the ethical issues associated with NBS by the academic literature. Owing to their ubiquity in medicine as well as in ethics, the discussion will be framed along the paradigm of the four principles. Obviously, the complexity of the problems does not fit into any single conceptual paradigm. However, these macro-categories may help in grouping the problems and may also show the relationships among them in a new light.

Beneficence

The oldest and most fundamental value of medical ethics is beneficence. Beneficence means that the doctor should act with the intention of doing good to the patient, and his action should be based on his professional knowledge and best judgment. The benefit in question is health related; the doctor is not committed to promote the financial interests, reputation or many other patients' interests, but to benefit his or her health. Therefore, without the presumption of a medical benefit, there is no justification to any medical intervention.

Sometimes this straightforward assumption may not be so clearly specified in concrete situations. The scope of health and of the statistical chances of affecting it must be predetermined prior to the assessment of the benefit inhered in any medical intervention.

The paradigmatic benefit in Western and other cultures is not directly medical. It is the "good Samaritan" kind of situations, in which one's life is in immediate and evident peril and the means for saving it is available and burdenless. Rescue of a drowning person is emblematic of such situations, also known in secular ethics as "the rule of rescue" (McKie and Richardson 2003). The maturation of the bio-psycho-social model of health in the 1970s and 1980s also stretched the notion of "medical benefit" by casting the very same idea of health as a complex, thick concept that calls for a holistic approach, in which psychological and social aspects play central roles.

From its very beginning, newborn screening has been motivated by the evident and direct medical benefit to the health of a baby when his or her pathological condition is detected while still asymptomatic, and a prompt intervention drastically reduces morbidity and mortality. At the time, in the eyes of the promoters of NBS, its benefit was self-evident as situations of rescue (Cookson, McCabe, and Tsuchiya 2008).

The classical justification for newborn screening was the idea that screening test should be performed when effective treatment is available for the conditions thus detected. This justification is supported by many official bodies and relevant positions that were published since the seventies. The key reference that addresses the criteria for screening is the seminal monograph that the WHO commissioned to Wilson and Jungner in 1968, titled “Principles and practice of screening for disease”. In this publication are present the classical “ten criteria for inclusion” of a disease in a screening program, already discussed in the previous chapter. More specifically, the second criteria states that “there should be an accepted treatment for patients with recognized disease” (Wilson and Jungner 1968, 26). The centrality of this principle is further underlined by the authors:

Of all criteria that a screening test should fulfill, the ability to treat the condition adequately, when discovered, is perhaps the most important. (Ibid, 27)

In 1968, when they wrote their seminal monograph for the WHO, Wilson and Jungner did not have newborn screening in mind; nevertheless it soon became a key reference for newborn screening as well, turning to be the starting point of any debate on the inclusion criteria for any new condition in newborn screening programs (Frankenburg 1974). In 1994, the Institute of Medicine’s (IOM) Committee on Assessing Genetics Risks Report recommends that “newborn screening only takes place (1) for conditions for which there are indications of clear benefit to the newborn, (2) when a system is in place for confirmatory diagnosis, and (3) when treatment and follow-up are available for affected newborns” (IOM 1994). A year after this publication, the American Society of Human Genetics and the American College of Medical Genetics also affirm that “timely medical benefit to the child should be the primary justification for genetic testing in children and adolescents” (ASHG and ACMG 1995, p.1233), statement that was reiterated in the

1997 Report of the National Institute of Health (NIH) Task Force on Genetic Testing (Holtzman and Watson 1997). In 2000, the American Academy of Pediatrics also affirmed that among the criteria for inclusion of a screening test for newborn screening is that “ the treatment for the condition is effective when initiated early, accepted among health care professionals, and available to all screened newborns” (AAP 2000, 394). In all these official bodies, as well in many other publications, the direct medical benefit to the newborn child tested is paramount and indispensable criteria for the inclusion of a disease in a newborn screening panel.

This conceptualization of benefit in newborn screening - “direct medical benefit” - is comprised of at least the following assumptions:

- a) it is individual – it is related to the specific baby that is tested positive;
- b) it is direct – the existence of a specific and effective treatment prevents the harm that would otherwise affect the child;
- c) it is immediate – since timing is a key element of the intervention, the very same treatment in a later phase would be less effective or even meaningless.

The progressive expansion of the number and of the characteristics of the diseases within the “new newborn screening programs” (i.e. the expanded programs) has entailed a parallel process of expansion of the concepts related to it, first of all, the concept of benefit and of these three assumptions.

In this light, the first criticism to the “traditional” concept of benefit focuses on the "restricted interpretation" of benefit when it is considered synonymous with "medical benefit". This seems to be a reductionist interpretation that casts a shadow over a more complex and nuanced concept of health. In fact, if benefit is only medical benefit, then treatment is the effective therapy that significantly affects the natural history of the disease. This is, for example,

how dietary therapy for PKU – the paradigmatic case of NBS – works. Yet, if we compare treatment for PKU with that for other diseases included in many expanded NBS programs, we start noticing some differences. Whereas dietary therapy for PKU practically prevents all manifestations of the disease, other conditions do not have a treatment that is so effective. There are treatments that work only partially or only on some but not all patients (e.g. diet for hypertyrosinemia and various lysosomal storage diseases – Ross and Wagoner 2012). There are supposedly afflicted children who do not become sick at all, or recover without treatment. Since the relevant “diseases” or conditions are extremely rare, it is quite impossible to trace out their natural history, and the overall impact of treatment. If we behold "effective treatment" as one that prevents all the manifestations of a disease, only 4 diseases out of the 78 conditions recommended by the American College of Medical Genetics (ACMG Report 2005) have such "effective treatment": congenital hypothyroidism (thyroxine treatment), biotinidase deficiency (nutritional intervention), phenylketonuria (PKU) (nutritional intervention), and medium-chain acyl-CoA dehydrogenase deficiency (nutritional intervention) (Bailey et al 2006). Moreover, some treatments are specific (e.g. low phenylalanine diet to children who cannot metabolize phenylalanine); while in other cases the treatment available is non-specific and supportive.

It follows that the construction of “benefit” requires mapping out efficacy along an axis of relevance (i.e. to what extent the effect is specific to the key manifestation of the disease) and an axis of power (to what extent the therapeutic goal is achieved). One may suggest a third axis that measures the duration of efficacy in time. It follows that it is virtually impossible to come up with a satisfying analysis of “benefit” to the very rare conditions relevant to expanded new born screening programs.

In order to support the expanded program, authors were in need to expand first of all the concept of benefit. The first official body that expressed to this idea was the National Research Council (NRC) that in 1975 opened its report by affirming that newborn screening is appropriate when it provides “substantial public” benefit, explicating it as benefit to the infant, to the family and to society (NRC 1975, 1). Indeed, with the development of DNA technologies that may apply to NBS, a former senior director in the NIH, Duane Alexander, and a senior director in the U.S. Office of Health and Human services, Peter van Dyck express their reservations with the concept of direct medical benefit, affirming that, among the major objectives that need to be addressed in the immediate future is:

The dogma that it is appropriate to screen only for conditions for which effective treatment already exists need to be changed, by broadening the concept of benefit from screening for the child to include the family (Alexander and van Dyck 2006, S351).

The American College of Medical Genetics Expert panel gives much support to a broadened concept of benefit (ACMG 2005). In its recommendations, the panel identifies 29 “core conditions” that fit the Wilson and Jungner criteria for screening. However, inclusion of 25 secondary targets ushered in a broader concept of benefit, even when a direct medical treatment is not available. In such cases the rationale behind NBS is the benefit associated with better general support to the child, the value of reproductive decisions by the family, and the benefit to society from improved understanding of the condition (ACMG 2005). Alas, this broad concept of benefit was assumed with the complete absence of social, ethical and legal considerations of expanding NBS programs (Botkin et al. 2006).

This gap brings forth two opposing lines of argumentation. First, we find some groups of parents that actively lobbied their state NBS programs in order to include screening of conditions

without any effective treatment, affirming that early diagnosis is a good in its own right. In their opinion, although such information might not bear directly on the medical benefit of the child, it is a valuable knowledge for the family as a whole. First of all, early diagnosis will prevent the "diagnostic odyssey" that parents and child would otherwise undergo in order to understand the symptoms and the overall health care situation in hand. Second, this knowledge may help them establish early coping mechanisms and psychological strategies of adaptation, reframing expectations and adjusting plans for the future. The alternative line of argumentation would be that a universal and mandatory healthcare program must stick to the highest standards of "evidence based" and consensus based benefit. Ironically, precisely when the era of "evidence based medicine" broke out (early 1990s), setting more rigorous standards on the notion of "medical benefit", the cotemporaneous expansion of newborn screening has stretched "medical benefit" away from standards of certainty (Moyer et al. 2008). Evidently, precisely because of their extreme rarity, it might not be ever possible to come up with "evidence based" standards for screening and care for many of the relevant conditions. This might lead to an absurd conclusion that certain medical conditions should be neglected (i.e. no action taken in regard to them) only because of their rarity. Expanded newborn screening programs embody the opposite attitude of commitment to act in the benefit of such rare conditions. Even though one may regard this commitment as one more dimension of "broadening" the conceptualization of benefit, it is also evident that policies on these very rare conditions must have some scientifically informed criteria in the spirit of "evidence based medicine". Put in other words, the question in hand is not about the proper conceptualization of "medical benefit" but, the construction of "benefit" in the context of such a public health program.

Because, ethicists and patients disagree whether such knowledge is beneficial or harmful, making a policy on such issue for every newborn child seems like a mission impossible. Arguably, like in other difficult choices, parents are expected to act according to their understanding of the benefit of the child. However, there is an evident conflict of interest between parents and baby with regard to the possession of such information. Besides, many – perhaps most – parents may not have a clear answer to the problem and may expect policy makers to come up with some recommendations prior to the implementation of a universal and mandatory program that generates information on carrier status as a side effect.

Some authors have moved from the basic concept of "benefit" to a more sophisticated term, "presumptive benefit" as one that better fits cases such as the detection of conditions that cause developmental disabilities and that do not currently have "medical treatment" (Bailey, Skinner, and Warren 2005). A case in point is screening for Fragile X Syndrome, a genetic condition that entails incurable mental retardation whose severity ranges significantly among patients. Early knowledge and intervention have proven to influence positively child development and to help supporting the family adaptation process to the disease (Bailey, Skinner, and Sparkman 2003; Bailey et al. 2008). Some call this general goal with the expression of "improved family's quality of life" (Burke, Laberge, and Press 2010; Bailey, Skinner, and Warren 2005). The basic assumption is that parents prefer to know the sickness of the child, independently from other considerations such as existence of effective treatment. Therefore knowledge becomes a benefit in itself. It is noteworthy that the "benefit" thus construed entails both "broadening" (i.e. attention to benefit to family and society) and "presumptiveness" (i.e. no matter how construed, the benefit is uncertain). By now, the conceptualization of "benefit" has been twice diluted.

If it is agreed upon that knowledge is a good in its own right, then it might be argued that mere knowledge may justify screening. But such a conclusion is quite problematic for at least two reasons. First, much of this kind of knowledge is genomic, and consequently considered sensitive. Second, this sensitive knowledge is primarily about children. We must also bear in mind that the information elicited by screening cannot be classified as either beneficial or neutral. Unjustified screening for a genetic condition is not like unnecessary blood count. The information that is created by screening might loom large over the tested child, his or her future, and the family as well.

The question of genetic knowledge as a good in its own right gets entangled by the circumstances of knowing. A comprehensive review of numerous national guidelines and position papers elicited a consensus against pre-symptomatic and predictive genetic tests on minors (Borry et al. 2006). Even when parents request testing for the sake of relief of their own anxiety or in order to plan ahead for the future of the child, professional guidelines deem such reasons insufficient (Parker 2009). If consensus exists against testing children upon the individual request of their parents, it makes much less sense to incorporate such testing in a universal, and often mandatory, testing service such as newborn screening. Moreover, we may face the paradoxical scenario that if a parent who is known to be a carrier of a genetic disease wishes to find out whether her child is carrier as well, the consensus leans against testing; but when information on genetic carriage comes by, as an incidental finding of NBS, the consensus is that it must be communicated to the parents, even if they have never asked about it. Let's explore this position.

Many affirm that in NBS genetic information is acceptable only as "incidental finding", and not as a primary goal, but only a side-effect, a by-product of testing. This means that such knowledge is a byproduct of a test directed at different kinds of results.

Carrier status is a specific kind of incidental findings because of the implications on the procreation related choices of many family members. But it is not clear at all that awareness of carrier status, especially of very rare and mild conditions is beneficial. Almost all reproductive choices motivated by awareness of carrier status are morally controversial – avoidance of marriage or natural procreation, pre-implantation diagnosis and abortion. While some parents may value carrier information, others – perhaps those that did not screen for themselves in the first place – may be less pleased with this involuntary lesson from their child's newborn screening result (Wright Clayton 2010). Whereas relevant family members may benefit from the information on carrier status immediately, the tested child will have the chance to reflect on the subject and choose for oneself only many years ahead, when the medical and reproductive implications will have been much altered. In the meantime, it is either the parents of the tested child who bear the responsibility to pass on the information to other family members or the state will have the burden to communicate information of carrier status to the relevant persons.

Given the absence of direct health implications for the child, it seems difficult to justify testing children for carrier status. In fact, from a systematic review results a broad agreement that testing for carrier status should not be performed in minors (Borry et al. 2006). Now problems of inconsistency arise when such information is anyhow given to parents because of NBS. If keeping this information has been described as “unfair” to parents, and perhaps even beneficial for the child when he or she will face reproductive choices, nevertheless when parents wish to test the child for the purpose of knowing his or her carrier status, then it is generally refused to

them, on the basis that being a carrier of an autosomal recessive condition does not affect his or her health.

The very concept of medical benefit is principally objective. It does not make sense to state, on one hand, that non-testing for carrier status is in line with medical beneficence and, on the other hand, that if information on carrier status is accidentally available, it should be disclosed. It must follow that either the construance of benefit in the context of newborn screening is inconsistent or that “fairness” to the parents trumps over the “benefit of the child”. Moreover, once mere knowledge is considered a medical good (either ante or post testing), then, the criterion of “available and effective treatment” implodes. Hence there seem to be two possible ways of interpreting the duty to disclose. According the first, it is in the benefit of the child. Then, strangely, it is good only once it is accidentally known. According to the second, the duty to disclose incidental findings is a matter of either fairness or respect for autonomy even it is not in the benefit of the child. The odd outcome would be that there could be a duty of fairness that might be harmful to the child. We have to keep in mind that parents do not exercise autonomy (=self-rule) in relation to the child; but society trusts parental discretion as the best proxy to the child’s wellbeing and future autonomy (rights in trust – Feinberg 1992). When parents clearly fail this trust, the state takes over. Hence, it is not unreasonable to say that when it is in the benefit of the child, parents are expected to handle incidental findings, even if they prefer not to; and if it is against the best interests of the child, parents must not be informed, even when it is unfair, disrespectful, or harmful to their own autonomous choices. It is not clear at all that the parents exercise “a right not to know” when the knowledge is relevant to the healthcare of the child.

Over the time, NBS has expanded so as to include detection of infants that do not need *immediate* treatment, thus undermining the "emergency criteria" that had initially strongly compelled towards the universalization of the program. In certain cases, early detection would allow the child to benefit from specialized services, as it is in the case of CF (cystic fibrosis). But more problematic still is the detection of "late onset diseases", that report results about possible future susceptibility of developing a multivariable disease (Burke et al. 2001). Lack of knowledge of the future is part of human nature; the average person does not know when he or she will die and of what cause. It is not clear at all that such knowledge is desirable; that people want to live with the awareness of the maladies and disabilities that will afflict them towards the end of life. Hence, a hazy line separates the desire – even need – to be aware of an impending calamity and be ready to face it, and the mere awareness of the trouble that lurks behind one's distant future.

All these changes above described affected the overall expectations and initial goal of NBS, initially instituted as a public health emergency measure to prevent mental retardations and, sometimes, even death (Grosse et al. 2006). Once the expanded program includes conditions for which there is no treatment or the existing treatment is not urgent, conditions with late onset, and conditions of unknown clinical significance, then the "emergency" aspect keeps its validity only in a few specific cases. The wider is the spectrum of the conditions included, the smaller is the impact of the emergency criteria on the overall program.

Some conditions, such as Fabry Disease, usually appear after many months of life, but because some children suffer earlier, and diagnosis of the rare manifestations typically takes a long time, inclusion of such conditions in NBS programs makes sense. Immediate diagnosis is not a life-saving emergency, but early knowledge seems to be beneficial, and the only

opportunity to do so is by means of NBS. Hence, the term “late onset diseases” is kept for conditions that appear in adulthood and that early knowledge thereof bears no medical value, but only an uncanny awareness of trouble in the distant future. As a matter of fact, the only such condition known today is Huntington Disease, which is an autosomal dominant, lethal, progressive neurodegenerative disease that affects only adults. Because of the dominant pattern of transmission, most people at risk are also aware of it. It might be argued that testing is in the clear benefit of those who test negative – they will not grow under the gloomy shadow of this catastrophic condition. It is not clear at all whether those tested positive benefit at all. Rather, they are at a significant risk of being harmed by the stigma. Children cannot choose whether to grow under this shadow or not; but as mature adults they can choose whether to self-test. Overall, because of the potential harm to the more vulnerable (children who are actually affected by the Huntington gene) and because it is considered unfair to pre-empt a decision that can later be made autonomously, there is a very broad consensus against screening for Huntington.

Genetic testing of children for adult onset diseases should not be undertaken unless direct medical benefit will accrue to the child and this benefit would be lost by waiting until the child has reached adulthood. (NIH Task force for genetic testing 1997)

The waning of the “emergency” element in NBS policies is clearly associated with the “technological imperative” of the MS/MS machine. The “technological imperative” is a critical term used whenever the actual reason behind an action is the mere technological availability to do so. In NBS’s early years, policy makers wanted to expand the program, but it was too costly to do so, or a reliable technology was missing. With the advent of the MS/MS machine the addition of many conditions to the panel bears marginal direct costs and the results are of high quality. In such circumstances one may desire to take advantage of the circumstances of

screening and add more tests, simply because there will never be a better opportunity to find out many affected children.

A paradigm shift from “emergency” to a “unique opportunity to benefit [at marginal costs]” taps into the “fairness” mode of reasoning in a step by step process. We have seen that it is commonplace to hold that it is “fair” to disclose incidental findings, even when it is not desirable to search for them in the first place. In a similar vein one may argue that it is unfair to use the MS/MS machine on a very limited array of conditions, when there are good reasons to suppose that parents would be happier with more tests; that it is “unfair” to perform mandatory testing “only” on a limited set of diseases, when it costs you almost nothing to do more. Lastly, it may also be argued that even with regard to conditions whose nature is unknown, it is unfair not to offer the parents the opportunity of discovery, knowledge and research. The common denominator of these strings of argumentation is the presumption that medical testing is by default beneficial and that withholding this potential benefit from patients is unfair, even paternalistic. The mode of reasoning is quite evident from the ACMG’s Expert Group’s response to the Report of the Council on Bioethics. It is worth citing in some length.

The ACMG Expert Group began with the understanding that rather than screening for conditions categorized as secondary targets, the secondary targets were revealed by the screening technology or secondary to the diagnostic process. They determined that it was basically unfair not to reveal knowledge to the parents if early identification of an infant with a condition could be beneficial to the infant, to his / her family, and / or to society even beyond direct medical treatment. [...] Society could benefit from a reduction in medical diagnostic odyssey that is costly to the healthcare system and very difficult to the family and child. (Trotter et al 2011, 302)

The paradoxical outcome is that information that has initially been deemed medically unnecessary is now integral to a program committed to beneficence. Moreover, the duty to disclose this information is derived from a fiduciary duty to the family, and not to the tested child. The shift of attention from exclusive focus on the child (or the index person tested) to the immediate family, and then to society at large is borne out by the justification given to the duty to disclose information that is considered medically unnecessary to the child.

Although the ACMG precludes “research” from considerations of benefit, it endorses optional research protocols of newborn screening. Interestingly, despite the evident trend to “broaden” the conceptualization of benefit and allowing it to be merely “presumptive”, the ACMG Expert Panel explicitly reject the potential benefit of research as relevant for choosing conditions to screening. One possible explanation for the categorical exclusion of the benefit of research from the ever expanding notion of “benefit” in newborn screening is that research on human subjects has always been a very sensitive issue in bioethics, bio-law and public opinion. Since the Nuremberg trials of the infamous Nazi doctors, it has been very strongly established that research on humans must always be fully voluntary. The WMA’s “Helsinki Declaration”, which since the 1960s sets the ethical standards of medical research, subjects every medical research to a review board committee’s approval (IRB). Anything labeled as “research” cannot fit a centralized, mandatory program such as newborn screening. Indeed, the ACMG’s Expert Panel’s 2005 recommendations classify as “benefit” and not “research” the “opportunity for better understanding of disease history and characteristics, and for earlier medical intervention that might be systematically studied to determine the risks and benefits” (American College of Medical Genetics 2005, 20). This is an unprecedented hair-splitting differentiation between “knowledge of natural history” and “medical research”. One of the research scandals most

responsible to the bioethics of research on humans, the Tuskegee Syphilis Study, was actually a follow up research aimed at the understanding of the natural history of a disease, which at the time of the research's initiation, was considered untreatable. Obviously, we do not insinuate that the ACMG's position is unethical like the Tuskegee Syphilis Study was. But the ACMG's attempt to differentiate the search for knowledge on the natural history of disease from medical research flies in the face of the history and fundamentals of contemporary research ethics and law. It is explicitly opposed to the most recent WMA (Helsinki) definition of medical research,

The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). (WMA 2008, Section A, 7).

Regarding the expanded newborn screening programs, it may be observed that not only has the concept of medical benefit been "broadened" in scope and epistemological certainty, but the range of reasonable justifications has been broadened as well, so as to include "fairness" and the good of medical research. It is as if the "common good" may be counted as medical benefit, even when it is not in the benefit of the patient.

The "good" coming from NBS extends care for the individual to non-clinical benefit that includes also the family and society. The broadening of benefit towards the family, and the weakening of certainty regarding the benefit to the child, might slide into the reception of the family as the second or secondary patient in ways that might erode the primary commitment to the good of the child, whenever he or she is the target of a medical intervention. Additionally, once the direct link between treatment and benefit is loosened, the idea that the relevant benefit be circumscribed only to the individual patient also loses power.

In sum, the expansion of the newborn screening programs, thanks to the application of the tandem mass spectrometry technology, was initially welcomed as a "technical application" to an established public health policy that would improve its diagnostic capacity in terms of quality and quantity of the conditions screened for, without reflecting much on its consequences. Sociologically speaking, the program has been expanded in the light of the previous success and with the attempt of improving it, but practically, once the argument based on "emergency" and "direct benefit" to the "individual child" tested had faded, the overall program is facing the need of a redefinition of its goals, criteria and place in a democratic society. At this point it seems clear that once potential secondary benefits are explicitly taken into account in the overall evaluation of expanded NBS programs, then they should be balanced with potential secondary negative impacts as well.

As a concluding note, one may wonder whether the cultural implications of the "broadenings" of the "expansion" of NBS create the impression that genetic testing is by default good for the child, and that it is not genetic testing that needs special justifications, but refraining from doing so. Indeed, The President's Commission expresses a worry that screening for genetic conditions of any kind might become the default practice,

If the principle "screen only if you can effectively treat" is set aside and if the technology of newborn screening shifts to primary DNA-based multiplex platforms, such as gene chips or even whole genome sequencing, the stage will be set for a vast expansion in newborn screening. The new principle guiding newborn screening would then be "screen unless there is a compelling reason not to screen". (President's Council on Bioethics 2008, Ch.2, 27)

In this section on beneficence in newborn screening we have seen a major transition from screening as a kind of rescue - the most restricted, urgent and self-evident kind of benefit, towards new horizons in which screening to genetic or otherwise conditions, once possible, is taken as the default beneficial medical practice, which is curbed only by compelling reasons against screening. The enormous and unprecedented shift comes at a significant conceptual price – the broadening of “medical benefit” along various axes – the axes of care for the child, the axes of the patients of benefit and the epistemological axis. Along the axis of care, we move from “effective” and near-curative treatment, to general information that is believed to assist in coping. Along the axis of the patient of care, we move from commitment to the index patient (i.e. the person on whom the medical procedure is applied – the screened child) so as to include the nuclear as well as the extended family, and even society at large. Along the epistemological axis we move from the ideal of “evidence based medicine” to a pro-active approach that endorses every diagnostic test that might be possible to perform in relation to a possible “disease” as beneficial. This epistemological shift involves the ethically problematic blurring of the fundamental line between “clinical care” and “research”.

Non maleficence

The original expression of the principle of non-maleficence comes from the Latin "primum non nocere" and indicates that the first obligation of a doctor is not to harm his or her patient. It is a categorical expression that indicates the absolute prohibition to act in a way that might harm the person that needs help. This obligation comes even before the prospects of doing something good. In this sense, a medically promising intervention must not be prescribed unless the doctor can be reasonably confident that his or her intervention is safe and acceptable. Put in other

words, that the risk of harm is both proportionate and consented to by the patient. The proportionality condition is patient-dependent; a great benefit to many patients cannot justify a disproportionate harm to one patient.

A public health program such as screening seeks to identify potential patients among a group at risk. In neonatal screening, the population is all the neonates. Differently from other screening programs – where the risk factors are associated with the characteristics of the defined population – NBS places the idea of risk in the possibility of not finding the affected children. In this sense, it is the risk of "missing" some cases. Usually, when the risk is very low, public health policies tend to ignore it; but NBS has been construed differently. The lower is the risk to have a condition; the more pressing is the perceived risk of missing even a single patient. Hence, the first public screenings for PKU were not limited to those at risk (e.g. neonates with family history of mental retardation), but applied to every neonate within reach, so as not to miss even a single one. It seems that this is the unspoken criterion operative behind the universalization of newborn screening.

Historically, this process of inclusion and extension (all the babies in all the countries) has spread out from the USA. It was an argument based on justice – in terms of equality of access to health care – that became the main justification for a universalized practice and an attempt at a uniform panel of screening conditions. This conceptual shift from isolating a population group at risk for the sake of screening, to the idea of risk as inequality of access to the program – and ultimately diagnosis and health care outcomes – explains some of the peculiar aspects of newborn screening: the strong advocacy rhetoric of "saving life" and the very successful expansion of the program all over the world, at least in its first phase (1970s to 1990s). This expansion was supported by other technical aspects, such as the existence of a

reliable, simple and cheap test (the Guthrie card), the practical possibility of applying it to almost all newborn, since the socialized medicine had implication on the "new" habit of giving birth in a hospital, and least, but not last, the excellent health outcomes of treated children (such is the case of dietary treatment for PKU).

These very positive considerations were evidently overweighting the mild discomfort of pricking the heel of a baby in order to get just few drops of blood. Moreover, because at the beginning only two/three conditions were screened, also false positive results were numerically inferior to those that appeared later in the expanded version of the program.

Therefore, the intuitive balance of risk/benefit was clearly on the side of the screening program. Medically speaking, it was worth doing it, since little burden was placed on the babies and great benefit was expected for those detected. Moreover, it soon became a state-public funded program, where not only "justice" as equal availability was addressed, but it was also universally affordable in all developed countries. On top of this, the social responsibility for the health of children was a common cause where advocacy groups and the US government converged, leaving little space to considerations on autonomy. In fact, which parent would refuse such a mild procedure for such a great possible good? It would make little sense, similar to refusing a lottery ticket that the state provides you for free as a present for the birth of your baby.

This ethos and governance style of NBS consolidated during the 1960s and early 1970's, when its international success for the two conditions screened was almost uncontestable. Questions of harm hardly arose. Even though the problem of false positive results was already known (Rothenberg and Sills 1968), the overall balance was undeniably on the side of screening. The harm of side effect was negligible relative to the enormous benefit. However, with the expansion of screening programs and the parallel broadenings of the conceptualization of its

benefit, the question of harm has become pressing. First, with the expansion of tests and extension of population covered, the absolute number of false positive children has increased substantially. It is now estimated the rate of false to true positive results is 9:1 (Wilcken 2003; Wilcken et al. 2003; Botkin et al. 2006).

The less of the conditions screened is “life-saving”, the more problematic is the harm accrued by false positive results. In medicine, the harm of side effects is justified by the medical benefit conferred on the same patient. The person suffering from the side effect of a drug is the person benefiting from its therapeutic effect as well. However, the main harm associated with NBS programs befalls on those who do not benefit from it. In a purely utilitarian mode of reasoning, so long as the overall benefit outweighs the overall harm, this imbalance might not count as a problem at all. But clinical ethics does not operate under such a utilitarian scheme and does not allow the harm of some patients in the benefit of others. Rather, even very minor harm to one cannot justify even significant benefit to others. But in the expanded NBS programs, a minor harm to the many is produced by an attempt to save the few.

A possible track for defending NBS policies may follow Rawls’s notion of “the veil of ignorance”. Since parents do not know whether their future child carries a condition targeted by NBS, it is reasonable to assume that everybody agree to a NBS program with a high rate of false positive results, in order to save the few truly affected. In this sense, at the time of policy making, every child is both a potential beneficiary and a potential victim of a program that does not sacrifice the health interests of some for the sake of others.

The difficulty with this tract of reasoning is lack of evidence that the public would actually choose to accept the high risk of a minor side-effect for the sake of a very low chance of major benefit. We need either efficient public participation processes or opt-in informed consent

or both in order to validate this assumption and act upon it. This is not an easy task, because the complications associated with false-positive screening tests are many and subtle.

One of the earliest reports described chronic anxiety and uncertainty regarding the child's health even after the false-positive nature of the test had been clarified (Rothenberg and Sillis 1968). We do not know how many parents develop such a response, but research shows that only one third of parents understand the meaning of "false positivity" and the reason why their child needed a second test. The main operative conclusion of these studies is that patient information and education are imperative. We wish to argue that without effective process of patient education, there cannot be a valid informed consent, let alone a presumptive one. Admittedly, when parental anxiety is isolated from other aspects of "false-positivity" in NBS, recent research has found out that almost all parents suffered some anxiety, and that virtually all stated that they would submit another child to screening (Beucher et al. 2011). Even though such findings lend support to the argument inspired by Rawls, it might be still unethical to conduct NBS without additional efforts aimed at harm reduction. This might require stringer commitment to patient education and to informed consent processes.

An additional difficulty in the formation of both public reason and individual choice is lack of data of the absolute numbers of "clinical false positive". A "clinical false positive child" is a child whose parents were contacted as a result of positive NBS test, but ultimately the baby was found not to be affected by the suspected disease. Based on reported lab standards and computer modeling, Tarini and colleagues have calculated an annual USA rate of false positive children ranging from 2,500 to over 50,000 (Tarini et al. 2006, 451). It follows from this estimate that lack of transparency regarding false and true positive testing is an ethical issue in its own right.

It is very difficult to evaluate the meaning and overall impact of some of the reported adverse outcome of false-positive screening tests, such as parents' negative perceptions of their child's health, parental stress, and parent-child relationship (Tluczek et al 2011; Gurian et al. 2006). For example, reactions to false-positive hypothyroidism results were found to be sleep disturbance, maternal crying, and infant feeding problems (Bodegard et al.1983). Increased parental stress and altered parent/child relationships were also documented in screening for cystic fibrosis (Baroni et al. 1997; Tluczek, Orland and Cavanagh 2011), hearing problems (Clemens et al. 2000), and metabolic disorders (Fyro 1987). Parents tend to be overprotecting, remaining very vigilant and alert to any physical symptoms of their child. Many studies report an increase in the number of emergency room visit, and hospitalizations for the infant (Gurian et al 2006; Fyro and Bodegard 1987; Bodegard et al. 1983) Since decisions about hospitalization are not in the hands of the parents, it is evident that somehow experienced doctors are also entangled in the reaction to "false-positive" results as if they bear some clinical significance.

Whereas the correction of ordinary "false-positive" results is a matter of days, the ultimate validation of some screening tests takes longer periods of time. Often, it is not clear whether validation of a positive result will ever occur, because many screening values fall beyond pre-set normal range and do not always correlate strongly with pathological categories (e.g. disease, syndrome, disability). Stefan Timmermans and Mara Buchbinder refer to asymptomatic babies who tested positive in such a manner as "patients in waiting". They are treated "as if" they were patients by their families and care givers, who monitor closely for any sign and symptom that might harbinge the advent of a catastrophic "diagnoses" of the suspected condition and tend to overprotect their health generally (Timmermans and Buchbinder 2010). In this group of patients the boundary between "false" and "true" positive becomes blurry. The only

true positivity remains a certain biochemical or genetic marker whose health-impact as yet to be revealed. As a matter of fact, such children may be considered subjects of research rather than needy patients. It is not unlikely that not only are “false-positive” babies and their families being harmed, but that some “true-positive” babies are also subjected to more harm than benefit, mainly through unnecessary treatment, follow-up and material and psycho-social burdens.

Two factors often aggravate the problem of false-positivity and “patients-in-waiting”. The first is the discrepancy between the universal drive of NBS programs and the real rarity of the risk. As Timmermans and Buchbinder observe, during the very same conversations parents may be “reassured” that the positive screening test is most likely “false-positive” and at the same time be urged to retest the baby immediately. The second kind of aggravation appears when a positive screening test is presumably associated with a devastating pathology such as mental retardation and sudden death. It is unreasonable to inform parents about such a possibility, however rare, and to expect them to behave on the assumption that “most probably nothing will happen”. But many parents check more and their searches in the web often fishes out worst case scenarios and plain misperceptions (Hewlett and Waisbren 2006).

In sum, the problem of non-maleficence in NBS ranges far beyond the mere balance of medical benefit and side effects. This is so because a) the relatively significant side effects are the burden of those who do not benefit from the program, because b) many more (in the range of 9:1) pay the price, even if minor, relative to the few that may benefit from it, and because c) it is not clear at all that those who test positive actually benefit (e.g. “patients-in-waiting”). When NBS programs began, the framework of rescue dwarfed the discourse on harm. But even when the harm side lacks any power to tip the balance against the screening program (e.g. the paradigmatic case of PKU), society has still the duty to divert efforts towards harm reduction.

One possible track of legitimization is by means of choice behind a “veil of ignorance”. When parents do not know yet whether their own child is going to be affected by NBS (i.e. to be tested either true-positively or false-positively) they might endorse the public health structure that governs NBS. However, so far, this mode of reasoning enjoys inchoate empirical support, it does not eliminate the moral duty to reduce harm and it does not preclude the possibility that people would choose otherwise, if more data and information become transparent.

We have argued that the “broadening” of the concept of benefit of NBS must entail the reciprocal “broadening” of our sensitivity to harm. If better parental coping capacity is a kind of benefit that merits screening, then increased parental anxiety is the kind of harm that must be taken into consideration as well. If improved knowledge of rare conditions is a social benefit justifying screening, the burden of increased hospitalization must be taken into account as well. This is not an easy task. As a “life-saving” enterprise, NBS began as an operation that is focused on its mission, not being concerned with broader medical and social issues. The only risk a rescuer knows is the risk of missing one salvageable victim, not the collateral harm that may cost to society. But the expanded NBS programs cannot proceed in this manner. Much of it cannot fall under the title of rescue; much of it is of questionable benefit to the individual. Taking the harm of NBS into consideration is especially tricky since it is quite difficult to assess holistic psycho-social implications, especially when much data is not yet transparent to the public.

Autonomy

Respect for personal autonomy is a fundamental bioethical value. Some authors refer to it as “first among equals”. It marks more than other values the spirit of “bioethics” relative to traditional and non-Western systems of medical ethics. Generally speaking, respect for autonomy

is respect for the choices of people in matters pertaining to their own good, mainly, life, health and body. In earlier times, it was assumed that health is an objective good, and professional doctors know best how to promote and protect it. It was also assumed that illness and suffering cloud the judgment of patients. Altogether, it was taken for granted that doctors' responsibility is to make the health-care choices on behalf of their patients, who, in return, are expected to comply. In this scheme, the doctor is active and the patient is passive. However, a new moral sensibility has altered this ethos of care. Contemporary bioethics and biolaw posit that 1) the idea of health also depends on the subjective perceptions and judgments of patients, that 2) unless proven otherwise, all patients possess the capacity for conscientious decision-making, and that 3) sometimes respect for the personal choice of the patient might bear a higher moral and legal status than the protection of his or her health.

The doctrine of informed consent is emblematic of this sensibility. Sixty years ago, formal informed consent did not exist at all; today in virtually every jurisdiction in the world, doctors must not treat a patient without either explicit informed consent or a presumption of consent, which is recognized by the law.

It is crucial to bear in mind that not every choice made by a person is relevant to the value of respect for personal autonomy. In Greek, "auto-nomos" means self-rule by means of self-legislation. Therefore, autonomy is clearly limited to choices regarding the self, and to rational, conscientious judgment. When a person cannot make such judgments, then caregivers recur to what it is called "proxy decision making". The idea is that another person may take the responsibility for expressing a choice for the patient. In the context of child care, the parents are considered the "natural proxies" of their own children. The healthcare professionals inform the parents about the health-care related choices at stake, and the parents may take the decision –

sign the informed consent, for example. Although the doctor – parent interaction is structured very similarly to the doctor – patient interaction, it would be misleading to say that the parents take over the “autonomy” of the child. In the context of child care, the use of the value of autonomy is always problematic. Self-directed choices by children are not considered rational and judicious enough. But the power of choice given to care-givers cannot be a power to decide for oneself. It is the responsibility to decide for a vulnerable other – the child (Buchanan and Brock, 1990, Ch. 5; Pediatrics 1995).

Indeed, regarding children, there are different meanings to the structures otherwise associated with respect for autonomy. Because parents care for and know their child better than any other person, it makes sense to say that parental choice is the best representation of the good of the child. On this point, the value is not autonomy, but beneficence. It is assumed that even if doctors and other caring people might think otherwise, the parents know best. However, since the motivating value is beneficence and not autonomy, it follows that whenever society has compelling reasons to assume that parental choice is not in the benefit of the child, there is no moral duty to respect it. Rather, society may have the responsibility to take over parental responsibility and decide on behalf of the child. This approach is rooted in the *parens patriae* doctrine which originated in medieval common law. According to this principle, the Crown (today: the state) is the ultimate proxy bearing responsibility for the wellbeing of the incompetent persons in its jurisdiction. The parents, as well as other guardians, are mere agents of the state, exercising their intimate acquaintance and love for the child in his or her benefit and in the name of the public.

An alternative or complementary meaning of “autonomy” in child care is not about the liberal value of personal autonomy, but the old attitude of granting autonomy to religious and

cultural minorities to exercise jurisdiction over family affairs, such as education and schooling. In this context, respect for parental choice would encompass choices made in line with communal values and on the assumption that children wish to be educated according to their culture's values.

The third possible meaning of “autonomy” in child care is related to the value of respect for personal autonomy. Since children have a potential for future autonomy, their caregivers and environment has a special set of duties to the future autonomy of children. Joel Feinberg calls this situation “autonomy in trust”, meaning, that children should be cared for in manners that empower their future ability to choose freely and conscientiously for themselves. Generally speaking, this implies two kinds of duties – duties not to harm future capacity for autonomous life and duties not to preempt significant choices which the child will be able to make as an adult (Feinberg 1980).

In sum, in relation to decision making for children, the notion of autonomy bears three distinct, even if complementary and overlapping meanings. The first is rooted in the value of beneficence, the second in the value of multi-culturalism and religious tolerance, while only the last appeals to the value of autonomous life and the duty of society to respect the future personal autonomy of every mature individual.

Is there a place for “autonomy” of any kind in a NBS public health program? Shall NBS be performed in a mandatory frame or full informed consent should be sought?

There is much variability in the framing of NBS, historically as well as geographically. Historically, in the United States, for the first time a universal public health program was targeted at a rare condition, and it became mandatory in many states, even though it involved neither contagion nor other threats to the public. Even today, in most states in the USA the

program is mandatory. But in two American states and in some countries, such as New Zealand, NBS requires full informed consent. Many different variants of informed consent schemes are in between these two extreme options (mandatory without exception and full informed consent). Some states divide screening into mandatory and recommended tests; other countries accept refusal of screening only on the basis of religious objection (Ireland), or have some others “opting-out” formats, such as making parents sign a dedicated refusal form (Israel). On top of different schemes of consent, and independently from the specific legal structure in which NBS program is framed, information is prerequisite to any consideration regarding autonomy. In fact, there is no meaning to consent/dissent without appropriate information related to it.

When the NBS program started, it was incorporated in childbirth care. After the second war world, birth progressively moved from home to hospital setting. Childbirth in a hospital was organized according to routines based on standards of hygiene, safety and prevention. Birthing women stayed in the hospital with their babies at least a week after birth (DeVries 1996, 49). Therefore, the earliest opportunity for testing coincided with the baby stay in the hospital. Formal informed consent did not exist at the time, and screening was introduced as an additional risk-free essential measure that nobody doubted. Later on, when informed consent became part of good care, the mandatory aspect of NBS was questioned also for life-saving testing. The fundamental question is when does refusal of parents to medical test of their child can be considered by society as disposed against the good of the child? Or, put in other words, when is the price of coercion worth imposing?

If the health risk of the child is a) immediate, b) substantial, and c) high, society tends to invest in coercion. But when one of these three factors is absent, society may avoid coercion. This does not necessarily reflect an attitude of respect for the decision of parents, but an overall

aversion to coercion. This aversion might be motivated by practical difficulties in enforcement or by excessive costs related to it.

NBS involves a unique combination of factors: it is immediate, it is substantial, but the health-risk of non-performance is very low. However, the price of coercion is also very low, because it requires one time simple intervention on an already hospitalized “patient”. Although the expansion of NBS weakened the immediacy, substantiality and probability factors, the very low price of involuntary policy facilitated the continuation of screening as a mandatory practice. Since the public either was not aware of the practice or did not object to it, no coercive measures were involved. Until this very day, the average person perceives of NBS as part of ordinary and voluntarily chosen healthcare service. Only when society has become sensitive to the moral price in terms of privacy and exposure of babies to large scale bio and data-banking, did the discourse on informed consent to screening started to gain currency.

If NBS is framed as a mandatory preventive health measure, there is no strong presumption against screening, because society does not leave any space for personal choice. One possible objection might come from religious conviction. Screening does not violate the norms of any known religion, but, historically, only religious values have been recognized as possible justification for some deviance from good standards of medical care for children (Laurie 2002). However, if some aspects of screening are framed as optional medical tests, then parents must act in the name of their child’s benefit, and his or her future autonomy, by making a choice.

Since informed consent is essential even for evidently beneficial medical services, it has been argued that NBS should be conducted with full informed consent. However, if there is no reasonable presumption against screening, why shall we ask for informed consent? It seems that in such cases, informed consent is employed as a token of respect for human dignity, as a

measure ensuring that people are not treated without their knowledge, without granting them the opportunity to ask questions, or to do something if they sense some problem and take an initiative about it. In this sense, informed consent allows the exercise of parental responsibility over NBS.

As we saw before, in some jurisdiction parents may “opt-out” from a default screening program. This seems to be a compromise between two kinds of policies. When full informed consent (opting-in) is needed, many parents may express some doubts, where professionals have none. The very nature of asking make parents more aware of the procedure performed, thus facilitating their refusal. This is why some professionals are against informed consent. Yet, the fear that informed consent policy might reduce actual rate of participation and, consequently harm some children, is both unethical and unsubstantiated. It is unethical because informed consent is not an instrument of compliance; it seems untrue because the few studies performed in order to establish the correlation between informed consent and participation in screening show that well-informed parents tend to accept newborn screening (van der Burg and Verwei 2012; New Zealand Research 2007). On the other hand, lack of informed-consent related procedure, would not be compatible with respect for autonomy, or, more precisely, with respect for personal parental responsibility for their children. Because, exercise of parental responsibility depends on the same psychological faculties and social empowerments that support autonomous choices, many people tend to think that parents exercise their autonomy when they choose for their children. However, “informed consent” to one’s own treatment and “informed consent” to the treatment of one’s own child involve different responsibilities. The latter requires stricter commitment to the good of the patient.

More troubling still are mandatory screening program that includes storage of data, storage of blood samples and the theoretical possibility of accessing those storages for research - all of this, without informed consent. Some states' programs, such as Texas and Minnesota, have been criticized and challenged at courts. In one compromise following such a legal action the Texas Department of Health Services destroyed over five million samples and a new state law empowered parents to request the destruction of their children's samples (Doerr 2010).

Parental informed consent to NBS is also problematic because of a potential conflict of interest. Once screening is justified by a "broadened" concept of benefit that encompasses "the good of the family", one may ask whether parents, who are part of "the family", can act as fair proxies of the child. In fact, if it is unclear who are the beneficiaries of a program such as NBS, parents might get confused about their expected role as decision makers. A typical example would be the "carrier status" information.

This kind of sensitive knowledge is irreversible – once it is known, it cannot be ignored anymore. Additionally, the presence of such information ramifies deeply and extensively into one's identity, conduct, social status and future. This may raise the question whether sensitive interventions which do not have a clear direct medical benefit should be performed within the framework of a mandatory universal healthcare program, and whether and in what ways people may exercise their right "not to know" certain kind of information. Some suggest that the child may be allowed to access certain kind of personally significant information once he or she reaches the age of maturity, thus allowing the adolescent to exercise his or her own autonomy.

Opting-in and opting-out strategies of informed consent/dissent have significant differences also in the kind of "activation" that each requires from health care professionals as well as from parents. In fact, while the first form requires the provision of information and the

responsibility of explanation by the health care professionals, who have the duty to actively search for consent, the second scheme puts the burden of the whole process on the parents' shoulders.

Since procedures regulated by informed dissent may be carried out in the face of patients' inaction, it is very difficult to know whether patients are indeed adequately aware of both, the procedure and their right to dissent. This is true especially in overwhelming circumstances such as childbirth. Patients' confusion may blight informed consent as well; but the requirement to actively sign an official form serves as a minimal safeguard against professional action which the patient would object to if he or she is given the appropriate circumstances of choice.

In sum, we can approach the principle of autonomy in NBS from three perspectives. The first is the different meanings of autonomy and the responsibility of parents to take decisions regarding the health and wellbeing of their children. In this context, the evaluation of the risk of harm to the baby, in case of refusal, should be balanced against the society's imposition on parents. Such balance may vary depending on the kind of benefit included in the evaluation – whether it is a low possibility of a direct benefit to the child or it is an overall unclear benefit to other stake-holders such as family members. The special circumstances of childbirth, combined with the rarity and complexity of the conditions screened for, render regulation by informed dissent quite problematic. Lack of reasonable and significant information is tantamount to malpractice, even if no harm follows. Therefore, whatever form is used to frame NBS, it is responsibility of the state and of the healthcare professionals involved in the practice, to make sure about the authenticity of parent's decision.

Justice

Aristotle says that "justice is the virtue of the virtues" or the supreme virtue. It has a key role in the relationships among individuals and between individuals and society at large. For Aristotle, justice is almost synonymous with ethics, since it indicates the "right thing to do". In the fifth book of the *Nicomachean Ethics*, Aristotle specifies two kinds of justice: distributive and commutative. The first one is about the relationship between the rulers and their subjects. The second one is about the relationship among individuals. From this distinction, different theories of justice, and the principle of justice that bioethics refers to, borrowed the term of "distributive justice" in order to indicate the issues of justice in health care.

The debate on justice in health care begins with a few basic assumptions. The first is that health care is costly and somebody must pay for it; the second is that this economic burden is constantly rising; the third is that the resources that each state dedicates to health care are not enough to cover all perceived health-care needs and that, therefore, these resources need to be rationed. Some will not receive all they might need; others will have to wait in line; sometimes the quality of the service might be lower than expected.

In order to understand and justify the expenditure needed for running a public health program such as newborn screening, we need to analyze the various levels in which distribution of resources occur. There is a basic level of distribution that is called "teleological", and indicates the "scope" for which certain amount of resources is dedicated (e.g. education, transportation, health, etc...). However, explicit and direct goals may indirectly but decisively bear on others, apparently unrelated ones. For example, it has been found that increase in women's literacy correlates strongly with decrease of infant mortality. Although education of women has its own independent justifications, and although it might sound morally questionable to educate women

for the sake of their babies, the undisputable impact on an important end-point such as infant mortality must not be ignored either.

Within the area of health care, resources are also distributed teleologically, according to domains of practice, such as primary care, hospice care, hospital care, public health. Although it is a matter of good management to use judiciously the resources assigned to each of these and other areas, the impact they may have on each other is already factored-in while talking about distribution of resources. A typical example related to public health is the impact of preventive medicine. The cost of "one patient" may be compared to the cost of a program that would avoid him or her to get sick in the first place.

Historically, the first public NBS was contextualized in terms of preventive medicine and asylum care, because a timely treated PKU child is a child saved from institutionalization for life. At the end of the 1950s, once dietary therapy for PKU was officially recognized, many hopes sprung to discover other treatments for the inborn errors of metabolism. It was believed that the way to decipher the mechanism of many diseases that cause mental deficiencies was open, and that one day, through NBS – early detection and therapy – inborn mental diseases would be abolished (Brosco 2011). In the historical part of this thesis, we have already witnessed the impact of the US government and patients' organizations on the development of the national mandatory NBS programs. In parallel to the advent and reception of NBS, an additional revolution in the public care for the “mentally incompetent” was taking place – the de-institutionalization of most asylum patients, a population that included people with “psychiatric” problems as well as mental retardation. One central motivation behind the closure of the big state-funded asylums was the marked increase in patient population and its related costs. In the mid-1950s, over half a million US citizens lived in such asylums (Sacks 2009). Any success,

even partial, in keeping these people in the community was considered of great benefit to both individuals and society. In relation to NBS and in addition to the evident humane goal of curing detected children, from an economic point of view it was now possible to “calculate” the value of NBS in terms of “life-in-an-institution” saved. Especially in the USA, medical care was considered a private responsibility; but care for the incompetents and efficient public expenditure were the duties of the state. Saving public moneys was a legitimate and uncontested justification for a state-funded NBS program. It was hoped that NBS and similar medical interventions would eliminate mental retardation similarly to what happened with the eradication of polio and pellagra by means of vaccination and education. But this hope has been thwarted. Despite unquestionable cost-effectiveness of the screening to PKU and hypothyroidism, the vast majority of mental disability remains mostly unknown and, yet, unpreventable. Just on the eve of expansion, the only official evaluation of cost-effectiveness of NBS determined the screening for PKU and hypothyroidism at the value of 3.2 million 1986 USD saved per 100,000 children screened. The US Congress Office of Technology Assessment, who conducted this study, concluded that additional screening tests are not likely to be cost effective, but if tests could be performed on the same sample it might be worth adding a few more conditions (Office of Technology Assessment 1988). Naturally, this research focused on the biggest practical and financial hurdle to expansion – the need to collect and process additional specimens. The arrival of the MS/MS technology shortly after the study, lent the impression that overcoming this particular hurdle would render expansion cost-effective. However, neither the OTA study nor others have factored in all relevant externalities such as the role of “false-positive” samples and the ensuing follow up of numerous healthy children (Pediatrics 2000, 418).

By the time that the dream of preventing all mental diseases by means of early detection and treatment dissolved, NBS was already a well-established public health program. Nobody questioned the necessity to screen newborns at least for PKU and hypothyroidism.

The debated changed perspective with the expansion of the NBS program, due to the introduction of MS/MS. In fact, as we saw in the discussion of the principle of beneficence, the expansion of NBS has been associated with broadening its scopes. Once we put aside the obvious “life-saving” screening tests, the scope or scopes of all other tests are not spelled out, in manners that facilitate the deliberation on the relevant resource allocation, direct and indirect costs as well as externalities. This lack of clarity has been aggravated by the central role of the MS/MS technology in the screening program, since the costs of one test are already partially covered by the spending on another. One can say that, once the infrastructure of a NBS program is already established, it is relatively inexpensive to add one more test – the sample is the same, programming the MS/MS machine is relatively simple, storage of sample is the same, as well as data report to the families/caregivers. But if among the consequences of adding “one more test”, we start factoring in other aspects, such as the exponential increase of false positive results, the consequent exponential rising of retesting, the need to parental counseling, and the long term follow up of patients, with conditions that sometimes have unclear diagnosis or unclear health impact on the child, the related expenses also expand considerably. This results in an overall underestimation of the overall true costs of NBS (Baily and Murray 2008). One aspect of this situation is the problem of harm (discussed in the section of non-maleficence); another is the economic burden of the overall healthcare expenditures that are produced by expanded NBS. Reference to the importance of evaluating the overall economic aspects of screening is present from the beginning even in Wilson and Jungner principles, when they affirm that “the total cost

of finding a case should be economically balanced in relation to medical expenditure as a whole” (principle n. 10).

The complexity of evaluating the economic worth of a NBS program is due at least to three aspects. The first one is the definition of the goal/s of the program – to save lives, to prevent disability, to reduce public medical expenditures or others. The second is to decide what aspects are significant to the goals and what are not – number of years, drugs, and days of hospitalization, follow-up, human resources employed, others. The third one is about how to factor in all these relevant aspects in a way that they can be weight up and compare – to define each item into discrete data and to balance them.

There are two ways in which economists and health policy analysts use to calculate the "value" of a program – cost benefit and cost effectiveness. The first one tries to monetize all the aspects. The second one compares "to do something" vs "not to do it".

In spite of strong affirmation of clear advantage of performing newborn screening, a few studies have systematically approached the subject, with no conclusive results. In the USA, one of the limitations for an overall evaluation of the economy of NBS is the patchwork nature of health care financing (Baily and Murray 2008). One study was performed in the UK, where the conclusion was that only two diseases were worth performing in the national panel, PKU and MCAD (Pandor et al. 2004). Similar results have been reported from Wisconsin (Insinga et al. 2002). For the rest, data are too skimpy to be evaluated.

The first financial decision that most states had initially to take was to dedicate certain amount of money to buying the technology necessary for the expansion. In 2013, a tandem-mass-spectrometry-machine costs around 500,000 US dollars. Once the MS/MS is in place, it can process between 400 samples/day, making a machine able to screen around 50,000 babies/year

(After the deduction of holydays and maintenance time). The maintenance of the MS/MS costs around 25,000 US dollars/year. In most places, a back-up machine is “needed” in order to make sure that there is no interruption of the constant chain of analysis. Evidently, the choice to purchase and maintain an MS/MS machine is a matter of macro-allocation – whether society dedicates this kind of investment to NBS. A second, subtler, question pertains to the specific *telos* of screening. If coverage of each and every newborn is part of its core mission, then a second machine is needed in order to back up the first machine. This is not a trivial observation. Even if it may be consider cost-effective to invest half a million USD in screening let’s say 90% of the neonates, it might not be cost-effective to invest an additional half a million in order to cover the remaining 10%. In addition to the marginal returns of the universalization of coverage of the screening efforts, expansion of screening tests is also implicated with very low marginal returns. A machine in "full profile use" is capable of detecting practically all the diseases identify by the ACGM (29 core conditions plus 25 secondary targets). Therefore, it appears that the consequences of increasing the number of the diseases make the difference in terms of economic impact of an extended program. In fact, when more diseases are searched for, there is an increased need of retesting positive results (confirmatory tests). In Europe, the average expense for the confirmation of a positive screening result ranges between 182 euro (UPD – UPD-galactose-4-epimerase deficiency) to 3.077 euro (GAII – glutaric academia type II) (Burgard et al. 2012).

We might observe that with the introduction of MS/MS and the expansion of the NBS program, a de-facto reframing of the conceptualization of screening takes place and has a direct impact on the overall evaluation of allocation of resources. From a lifesaving enterprise, it has been broadened so as to cover many possible needs of children, families and society; from an

evidently cost-effective investment, it has turned into a universal mission that is hardly sensitive to marginal returns. This is also borne out by many centers' extraordinary efforts to trace the few babies who are not screened by the routine procedures.

In order to discuss the “justice” aspects of NBS, we have to deconstruct the evolution of NBS in terms of its ultimate healthcare goal. With the individual testimonies of children who, owing to screening for PKU were saved from life in an institution, severe disability and even death, screening was represented as a “life-saving” enterprise in the spirit of the “rule of rescue” whose mission transcends opportunity costs. The change of context entails a change of operating paradigm. Preventive medicine is measured by cost-effectiveness; but effective rescue operations are carried out regardless of the costs (Paul 2008). The economics of life-saving operations are sharply demarcated in the sense that society does not set limits on rescue efforts out of considerations of future burden of care. Even though many CPR efforts are unsuccessful, for example, worry that resuscitation is likely to result in a long-term care of vegetative patients has never been an argument against resuscitation that might be successful. But as a public health measure of prevention, in line with Wilson and Jungner's criteria, the economics of NBS must be broadly and loosely demarcated, factoring in the “total” relevant costs, including externalities of any kind. Whereas it would be ethically possible to defend refrainment from screening of extremely rare conditions, merely on grounds of low risk, once the question is presented from the perspective of an individual baby in need of saving, his or her anonymous presence among million others shines out in the eyes of the public (Grob 2011, ch. 5). The search for the undiagnosed child with a “treatable” inborn disorder is perceived as the search for a lost baby in a forest or a drowning child in the sea. This creates a new challenge to the fundamental value of

the “rule of rescue” (or: the Good Samaritan). Traditionally, this rule applies in a very specific set of conditions:

1. An identified individual
2. A life-and-death crisis
3. An identified agent that can act
4. A realistic possibility to save this individual at low risk / cost to agent
5. Failure to act will almost certainly result in death or a comparable harm.
6. Typically, the agent confronts the victim (i.e. they are close enough for the agent to see / hear the victim).

In “life-saving” NBS, the “identified individuals” are babies with inborn catastrophic conditions. The agent is the state and is already operating NBS apparatus. The expansion of NBS appears relatively cheap, especially when externalities are not factored in. This framing extracts screening from the distribution pie of public funds, by signaling out NBS children relative to children that would be saved by means of investment in parental education and accessible basic health care. At any one time, we know that specific neonates, however few, are in need of NBS; but we do not know which one might die owing to lack of other healthcare services. This situation creates a powerful psychological appeal to behold NBS as a “life-saving” operation, even though refraining from action carries only a very small risk to every newborn involved.

We may observe that the expansion of NBS (at least with regard to certain conditions) has created an unprecedented “rule-of-rescue”-like situations. This is because although the beneficiaries of rescue are specific individuals (i.e. the neonates afflicted with treatable disorders), their identity is unknown at the time of rescue. Rather, the very nature of the rescuing action in question is finding out the identity of those in need. This new situation is borne out by

the case of Ben Haywood who died due to a very rare and undiagnosed metabolic disease – MCADD. His father heralded a campaign that resulted in a new NBS law in Mississippi that mandates one of the broadest screening panels in the USA. Ironically, at the same period of time, infant mortality in Mississippi, one of the poorest states in the Union, was rising (Baily and Murray 2010). Apparently, the story of one child with a discrete inborn condition has greater sway over the public than the stories of hundreds of unknown children whose poverty and social deprivation contribute to their deaths.

The question whether NBS is a “life-saving” operation bears on another aspect of justice as well. A major factor behind the expansion and universalization of NBS was the pressure generated by activists and professionals in the name of “fairness”. It has been repeatedly argued that it is “unfair” that a child born in one jurisdiction die from an undiagnosed disease, whereas the very same baby would have been saved had he or she been born in a hospital a few kilometers away.

But there is something odd in this mode of reasoning. After all, federalism and state sovereignty are about diversity in communal choices. It is in the nature of democracy and cultural diversity that one community invests more in certain services, such as education, than in others, such as road safety. If "fairness" in public services meant "uniformity", little is left for local decision making.

We believe that two factors account for the centrality of "uniformity" in the currently prevailing trends in NBS policies. The first is the association between “uniformity” and "harmonization". Whereas the former is associated with the justice discourse, the latter invokes the scientific values of standardization of lab procedures, reproducibility and generation of comparable data.

The second factor is the “urgency narrative” underlying all NBS policies (Grob 2011, 191). Whereas pluralism in democracy accommodates diversity of public services, the common denominator of respect for human life pushes all communities towards uniform standards of emergency life-saving services. Perhaps the key to understanding the success of the “fairness” argument in NBS is its “life-saving” categorization. While democratic regulations mean fair procedures (e.g. one person/one vote, lack of discrimination) and openness to diversity of laws and services, “life-saving” operations imply substantive equality – a minimum level of services, such as universal and equal accessibility of rescue and emergency care. When the life of a baby is at stake, talking about money sounds mean; but when millions of babies are subjected to a medical procedure, however mild, as an “emergency measure”, the “emergency” becomes a “universal routine”.

Nowadays, the overall tendency is towards the expansion of NBS services. Uniformization and harmonization of NBS, at the national and international levels, are considered the hallmark of most developed countries, and the horizon of the developing ones. Investment in such health care enterprise should be accompanied by an overall evaluation of its cost-effectiveness, which does not prevent a community from paying more than its ordinary standards of cost-effectiveness, when this additional burden reflects awareness of society’s moral values.

CHAPTER FOUR: THE ISRAELI NBS PROGRAM

Israel health care system and the care of newborns

The state of Israel is situated in the east side of the Mediterranean basin and covers 20.700 km² (a little bigger than the area of the Veneto), with a population of about 8 million people: 6 million Jews, 1.3 million Moslems, 152 thousand Christians (Arabs and not Arabs alike), and 125 thousand Druze. In 2012, 170.980 newborns were registered. Life expectancy at birth is 82 years. Infant mortality is 3/1000. In 2010 Israel joined the OECD (Organization for Economic Co-operation and Development)⁸.

Until 1994, healthcare was provided through voluntary patients' clubs which acted as non-for-profit public insurers. Private practice was the lot of the few. Public health and some basic child-care services were the responsibility of the state. Since 1995, all Israeli citizens and residents benefit from universal mandatory healthcare coverage, provided by the old voluntary patients' clubs, which then became subjected to national regulation. Health insurance is collected in the form of special tax, whose proceeds are transferred to the public insurers according to an elaborate formula, factoring the number of registered insurers as well as some of their demographical characteristics. While health insurance tax is progressive and mandatory, every person has the right to choose his or her own insurer, and to switch among insurers periodically.

⁸ For more detailed statistical data on the country see:

<http://www.oecd-ilibrary.org/sites/csp-isr-table-2011-1/en/index.html;jsessionid=25gq0qxdkvehm.epsilon?contentType=/ns/KeyTable./ns/StatisticalPublication&itemId=/content/table/20752288-table-isr&containerItemId=/content/table/20752288-table-isr&accessItemIds=&mimeType=text/html>

Last date accessed 12.10.2012.

The law sets a minimum standard of care (“health basket”) to which all public insurers are committed, but, as part of their competition for membership, these insurers offer expanded range of services and sell broad packages of health insurance (Horev and Babad 2005). The 1995 National Health Insurance Law requires that the health basket be incremented every year following population growth and the need to introduce new treatments and technologies. Every year, the minister of health nominates a special “health basket committee” to determine which new such treatments and technologies be incorporated in the “health basket”.

Whereas clinical care is administered by independent non-for-profit corporations, childbirth, public health and psychiatric care have remained the direct responsibility of the state. Some of these services are available for every person universally, regardless of one’s legal status (e.g. vaccination and basic child care clinics). As customary all over the world, emergency health care is provided to every needy person regardless of legal and insurance status (Chinitz et al. 1998).

A pride of the Israeli health-care system is the chain of basic child care clinics called "tipat halav" (טיפת חלב) – literally "drop of milk" (Lazarus and Hersh 1977). These clinics offer periodic check-ups of babies, vaccination and counseling to mothers on various aspects of child care. Attendance is obligatory (but not vaccination), free of charge and available to all, including illegal subjects. In the early 1950s, when Israel was a young, small (Jewish population in 1948 was 600.000 people), and poor state, over flooded with nearly a million immigrants coming from poor countries, the “Drop of Milk” services helped reduce sharply and without precedent the rates of infant morbidity and mortality. This service also set up the scene for large scale mandatory and universal services of preventive medicine and early detection, with clear preference to neonatal and baby care. The “Drop of Milk” clinics served as cultural bridges

between the diverse groups of immigrants (e.g. holocaust survivors from Eastern Europe, immigrants from Iraq and Morocco etc.) and the state, especially its child care and mothers, on issues such as cleanliness, diet, children development and safety, and school attendance. The clinics were staffed by educated and well-assimilated professionals. Often, these professionals were themselves past immigrants from the same countries, hence, intimately familiar with the local language and habits.

Whereas the Jewish population had had functioning healthcare services, when “Drop of Milk” was established, it was the only healthcare service available for most Israeli Arabs, who then numbered in the range of a quarter of a million people.

The “Drop of Milk” network of services embodied a national policy of unprecedented preference to child care and to preventive medicine. A society that was not able to provide state of the art medical care to all of its population, conscientiously mobilized its meager resources in order to provide uncompromising preventive care for its pediatric population. Since then, Israeli economy, science and healthcare system developed rapidly. By the late 1960s, Israeli biomedicine did not lag behind Western standards. But the infrastructure and cultural ethos of comprehensive and centralized infant care loomed large over the early adoption of newborn screening and its contemporary regime of expansion.

NBS in Israel

In the light of the history narrated in the previous section, it is no wonder that in 1964, Israel was among the first countries to implement universal NBS to PKU (Cohen et al. 1966). In the beginning, screening started in Israel’s largest and governmental hospital in Tel HaShomer, near Tel Aviv, fast expanding so as to cover most Israeli neonates. This unprecedented success led to the hosting of the second international conference on PKU in Tel HaShomer hospital in 1969.

The infrastructure and healthcare ethos of preventive baby care and the screening lab in Tel HaShomer contributed to the early expansion of screening to hypothyroidism (Sack et al. 1985). Tel HaShomer hospital also established the first and only dedicated PKU and hyperphenylalaninemia clinic in Israel. Overall, the early phase of Israeli NBS was conducted similar to the “Drop of Milk” services – a national policy that was implemented uniformly but locally, since other hospital labs began to carry out the screening for PKU and hypothyroidism.

The expanded NBS era coincided with the transformation of Israeli healthcare by the National Health Insurance Law of 1994. Not only didn't the law grant any privileged status to baby care or preventive medicine, but the weakening of socialist values also facilitated pressure on “Drop of Milk” and other programs to size down, not expand. Public officials did not have any more the power to introduce cutting edge screening technology without approval of the national health basket committee. It was evident that screening for extremely rare diseases stood no chances in competition with anti-cancer and similar novel modalities over public moneys.

In the early 2000s, anonymized blood samples from Israeli screening were sent to the USA for analysis in order to map out the incidence of the screened metabolic diseases in the Israeli population. Once it was found out that the incidence was very similar to the US population and that Israeli babies could have been diagnosed, the motivation to expand NBS grew.

In 2005, a philanthropic Jewish fund donated money for the purpose of purchasing the MS/MS technology that will serve an Israeli expanded NBS program in Israel. The Ministry of Health structured the expanded NBS as a hybrid of disperse, community based service and a centralized and unique lab and database. Responsibility for screening remained in the jurisdiction

of the Department of Community Genetics, but the screening itself was centralized and placed in a dedicated MS/MS lab in Tel HaShomer.

This program initiated in 2007 as a pilot and it operates as official program from 2009.

The advisory committee on NBS has not official status. No nomination writ has been issued and minutes are not taken down from its deliberations. As a matter of fact it is an informal ad-hoc body summoned by the general director of the minister of health in order to consolidate an incipient policy for the expansion of NBS. Members of this informal committee are the chair of the department of community genetics, the head of the central NBS lab, the chairs of the neonatology, endocrinology and metabolic diseases chapters in the Israeli Medical Association, and three prominent experts, one from the north, one from Jerusalem and one from the south of the country, as well as a lawyer from the ministry of justice. The information about this committee was communicated to us by the chair of the NBS central lab, Dr. Almashanu, who participated in its deliberations from the very beginning.

This mode of practice is typical of Israeli governance that tends to kick off new initiatives less formally and by means of improvisation. Formal regulation appears only in later stages of the service or operation.

NBS and the Israeli Law

The state of Israel was established in 1948 as a parliamentary democracy, without a constitution, but whose “basic laws” addressed procedural issues, such as the structure of the parliament and the governance of the army. Owing to tensions among different cultural and ethnic groups, especially between the religious and the secular streams of Judaism, Israel has never adopted a constitution. However, in the early 1990s a “constitutional revolution” has taken place in the

form of basic laws that grant constitutional rights to citizens. In this context, a landmark law is the Basic Law on The Dignity and Liberty of the Person (1992), which has paved the way and marked the values for all future regulation of issues relating to personal rights, such as medical care.

Israel inherited the legal system established by the British Mandate (1922-1948) as well as some old Ottoman laws that had survived into that Mandate. Secondary legislation regulating healthcare, such as the Doctors Decree and the Midwives Decree, were issued by the British Mandate. Israeli law has a special feature called *Baggatz* (It is a Hebrew acronym for “High Court of Justice”). *Baggatz* was also part of the inheritance from the Mandate, and was formulated in the Basic Law of Judgment (1952). This feature empowers every person to appeal directly to the Supreme Court in order to redress injustice done by the authorities and which cannot be addressed by another judiciary body. Many landmark rulings pertaining to civil and human rights have been issued by this procedure. Although no appeals to *Baggatz* have been made in relation to NBS, in case some parents perceive NBS or part of the NBS process as harming civil or human rights (such as it happened in some US states), parents might challenge NBS regulation by appealing to *Baggatz*.

The combination of *Baggatz* case laws and the growing body of basic laws on human rights create a regulative landscape within which the healthcare system tries to fit in, lest its practices be overruled by *Baggatz*. One recent example is a *Baggatz* ruling from September 13, 2011, which temporarily suspended a primary legislation withholding child support (in the range of 20-60 Euro a month) from parents who do not vaccinate their children. *Baggatz* gave a few months to the State of Israel to present its case and persuade the court that this new law is compatible with the fundamentals of natural justice and Israel’s basic laws and values.

Until 1994, Israeli medicine benefited from almost complete independence from primary legislation. With the exception of clauses on abortion in the criminal code (inherited from the British Mandate, which instituted in 1938 its Offenses against the Person Act) and the 1980 Anatomy Law, Israeli medicine was judged by professional perceptions of “good clinical standards”. Licensure, as well as other administrative activities, was regulated by secondary legislation in the form of Ordinances of the Ministry of Health.

During the last twenty years, a surge of primary legislation in healthcare has transformed the legal frame of Israeli medicine. The 1994 National Health Insurance Act established a minimum level of healthcare as a right of every permanent resident. The 1996 Patients’ Rights Act formulated the doctor-patient relationship in terms of rights and, for the first time, set standards of informed consent and other fundamentals of clinical ethics. In 1999, the Supreme Court ruled that violation of patient’s autonomy should be considered as compensable negligence regardless of considerations of harm (2781/93 נב). This particular ruling was handed down with regard to a medical procedure to which informed consent had not properly been obtained. It is noteworthy that the event in question took place before the enactment of the Patient’s Rights Law. This communicated two key messages. The first is that even harmless, or almost always harmless, interventions, such as NBS may be liable to tort litigation, merely on grounds of due consent (Paragraph 38 in the above ruling). The second message is that Israeli law approaches respect for autonomy in a broad, naturalistic perspective, rather than as a contractual obligation which is read according to the letter of the law.

In 2000, the Israeli parliament enacted the Law on Genetic Information which prohibited the performance of “any genetic testing” without full informed consent, and any genetic testing of minors without the informed consent of his/her guardian (Clause 24). The law defines

“genetic test” as “testing of a DNA sample with a diagnostic purpose” (Clause 2). This narrow definition does not cover NBS by means of non-genetic tests, such as MS/MS analysis, even though the information retrieved is often about genetic conditions. The gap between the spirit of the Genetic Information Law and NBS, and the obstacle this law has set on expansion of NBS to genetic testing, has led to an initiative to amend the law. Whereas consensus prevails regarding the need to address NBS by primary legislation, opinions vary with regard to the appropriate policy, for example, whether to exempt NBS from the restrictions of the law. So far no mature proposal has passed the initial phases of deliberations.

The first Ordinance addressing NBS was issued in 1999 (Ordinance of Medical Administration 16/1999). It specifies the obligation of hospital managers to oversee the technicalities of sampling and sending them to the national laboratory. There is no reference whatsoever to patient information and either consent or dissent. This Ordinance was replaced by another (17/2000), and three years later, by another one (52/2003). This chain of changes articulated increased bureaucratization of NBS (e.g. 16/1999 specifies six informative items to be written on the Guthrie Card; in 52/2003, there are ten). None of the issues raised by the ethical discourse on NBS was manifested, even implied, in these ordinances.

Ordinance 22/2007 merely announces the opening of the renewed NBS lab. Ordinance 2/2009 spells out the new screening policy. In its preamble (Clause 1) the ordinance refers to the expansion of NBS, the variety of NBS policies around the world, as well as the professional controversies pertaining to the process, without entering into them. The ordinance designates the physician caring for the pregnancy as responsible for informing the “woman/parents” about NBS, mentioning the informative brochure, which will be discussed later on (Clause 2.1). In case of elective home-birth, the mother should be made to sign a special form declaring her

responsibility for the screening according to the ordinance (Clauses 2.2 and 3.3). Parents who refuse screening should be informed by the physician responsible for neonatal care, and should sign a special refusal form. The hospital will then send a Guthrie card without blood sample, accompanied by the words “refused to screen” (Clause 4.2). A mother, who chooses to leave hospitalization prior to screening, should also be made to sign the refusal form. In such cases, the woman will be referred to the local Drop of Milk clinic for screening the child.

The ordinance lists the eleven conditions chosen for NBS, allowing the professional committee to modify the list as it saw fit. The ordinance is also notable for stepping up the bureaucratic hold of the NBS and its centralization. The number of data items to be written down increases to nineteen. The authority over follow-up of aberrant reports is placed in the hands of the department of Community Genetics. Criteria for becoming an affiliated center for follow-up are introduced.

Ordinance 17/2009, issued on April 20th, is the most recent and the one effectively in force. It contains two alterations relatively to the previous one (2/2009). The first is the addition of VLCDAD to the list of diseases screened. The second one pertains to home birth.

About 800 children (0.5% of live neonates) are borne in planned home birth, under the care of specially licensed midwives. In addition to the designation of the mother as responsible for NBS, and in addition to making her sign acceptance of this responsibility (Clause 2.2), Ordinance 17/2009 contains a new and long section dedicated to home birth (3.3). The caregivers have the duty to inform the mother (and father, if relevant) on NBS, inclusive of information on the risks and the availability of every neonatal and Drop of Milk clinic for performance of the tests, as well as on the possibility of retrieval of blood samples at home. The midwife and doctor (if one is involved in birth care) are responsible for monitoring compliance. If a healthcare

professional performs the sampling, she or he is responsible for executing it according to the Ordinance. The regulation of NBS in Israel deals with home-birth in great detail.

Ordinance 17/2012, regulating home birth, refers to NBS twice, even though NBS is unrelated to childbirth, and must be performed at least 48 hours after its completion. Interestingly, ordinance 17/2012 mentions neither patient information nor the procedure of opting out of screening. NBS is listed among the actions that the midwife must perform (Clause 6.5). As a matter of fact, the Ordinance obliges the midwife to visit the child two to three days after birth in order to take care of the screening test. This is especially odd, since the Ordinance also requires that the neonate be seen by a pediatrician within 24hours after birth. The Ordinance does not explain why NBS is a midwife's responsibility even after the baby has started routine pediatric care. Whereas Ordinance 17/2009 requires that refusal to screening be signed after an explanation is given to the mother/parents by the hospital's neonatologist, not only doesn't the homebirth Ordinance mention refusal to screening at all, but it also does not mention any pediatrician's involvement in the process of consent/dissent. By default, if the midwife is the only healthcare professional nominated as responsible for NBS, she is the one that will process refusal as well.

The expansion of NBS and its occurrence following the framing of Israeli medical law in terms of patients' rights, and within the context of a constitutional right to dignity and liberty, prevailed upon the Ministry of Health to address issues of patient information and informed consent within its ordinances. Although the Genetic Information Law refers to DNA analysis only, its shadow certainly loomed large over the NBS Ordinances. However, as a public health service, which developed before the era of rights, and whose very essence is universal coverage in the benefit of the few, NBS did not seem fit to ordinary informed consent processes. Indeed,

the Ordinance created, for the first time in Israeli law, a structure of informed dissent and obligatory choice. Even though patients are always empowered to refuse medical care, and even though parents have the power to object to vaccination of their children, the authorities have never formalized refusal to vaccination in the form of a duty to inform parents about the possibility of refusal accompanied by a dedicated opt-out form. Withdrawal from vaccination programs is a de-facto negative liberty, tolerated only. It has not been suggested in the courts that exposure of babies to the risks of non-vaccination is tantamount to child neglect that necessitates State intervention. (The last significant non-immunization related morbidity in Israel was an outbreak of measles affecting 1500 children in 2007-2008).

Although NBS does not carry any health risk at all (many people believe that vaccination might be harmful), the expansion of NBS has been accompanied with the legal structuring of informed dissent. This entailed a recognized right to opt out even from screening to PKU and hypothyroidism. The uniformity of consent-related regulation to NBS is especially interesting in the light of Clause 13(5) of the Patient's Rights Law, which requires that whenever a medical intervention "has a novel character", this novelty be communicated to the patient in the process of informed consent. Neither the Ordinance, nor the informatory brochure issued by the Ministry of Health (discussed below) distinguishes between the well-established NBS to PKU and hypothyroidism and the expanded panel. The professional controversies that are mentioned in the preamble to the Ordinance are not communicated to the public either.

It seems that the governance of NBS in Israel has incorporated elements of informed consent to the minimal degree necessary (according to the legislator) to pre-empt allegations of disrespect for autonomy. Whenever NBS is carried out according to the law, every mother should receive the relevant information, including her right to refuse. However, in opposition to

all other healthcare choices, in which inaction is the default track and action requires active consent (O'Neill and Mason 2007), NBS is the only procedure in Israeli bio-law in which the default practice is action and only inaction must be documented in the format of informed dissent. As said, an additional feature of the framing of consent to NBS is uniform approach to all screened diseases. On one hand it is evident that separate informed consent to each and every disease is impractical, on the other hand the packaging of expanded screening together with screening for PKU and hypothyroidism yields the impression that these two practices might be controversial as well. It seems that the authorities mobilize the broad acceptance of screening for PKU and hypothyroidism in order to recruit compliance with an extended screening panel; but this has been carried out at the possible price of weakening adherence to the traditional screening itself.

Legislation in Israel

1948 – Establishment of the State of Israel

1952 – Basic Law of Judgment

1992 – Basic Law on the Dignity and Liberty of the Person

1994 – National Health Insurance Act

1996 – Patients' Rights Act (including informed consent)

1999 – Supreme Court ruling. Violation of patient's autonomy, even without following harm, is considered negligence worth of compensation (tort law)

2000 – Law on Genetic Information (prohibition of any genetic testing without full informed consent)

The nuts and bolts of Israeli NBS – the actual process

In this section we narrate the actual process of screening as a top-down process of policy implementation. In each step, the responsible professional exercises considerable discretion. This informal, organizational knowledge of “know-how” has been obtained through personal interviews with the persons in charge of the Newborn Screening Center. Since Israeli NBS is highly centralized, it is safe to take them as reflective of the actual practice. In addition to the legal and formal documents analyzed and the interviews recorded, the following data is based on the annual report of the Israeli Bureau of Statistics (whose published data lag behind a few years) and the official report of the Department of Community Genetics on NBS in Israel (2012).

In Israel, most children are born in a hospital, while only a small, although growing, minority of women chose to give birth at home. There are almost 8 million people living in Israel. Every year there are around 170.000 newborn babies, only 800 of those babies are born at home (as planned home birth, to be distinguished from unplanned early delivery, following which mother and baby are immediately transferred to a hospital).

In Israel, ordinary childbirth is paid to the hospital directly by the National Insurance Agency. The agency transfers a fixed sum of 9000NIS (1800 euro) for every childbirth to the hospital where the child is born. This covers childbirth and hospitalization of mother and child for up to 72 hours (that correspond to a stay of at least two nights). Costs associated with special neonatal care, such as NICU, are paid by the health insurance of the baby, which is the mother’s insurer, or the father’s, in case the mother is uninsured. Since actual birth related expenses are much lower than 1800 euro, Israeli hospitals are in fierce competition over pregnant women, trying to lure them by means of private room, upgraded food and openness to complementary aids, such as aromatic oil massages. NBS is not paid by the “health basket” either. Since the

hospital costs are negligible, they are not covered specifically. The NBS unit operates as an arm of the Ministry of Health, and, like other public health services, it is a direct government service.

Routine neonatal care is comprised of two kinds of screening. The first is a local set of tests such as a general physical exam by a pediatrician, hearing test and, sometimes epidemiologically relevant blood tests, such as HIV and G6PD. The second panel of screening is the retrieval of a few drops of blood from the baby's heel. This is done between 48 to 72 hours postnatally. Only dedicated Guthrie cards authorized by the NBS lab are used (8.1) and they are accompanied by dedicated forms of the NBS center (6). These attached forms must be fulfilled with the relevant information required for each baby (following the last Ordinance, 19 items are required). The envelopes containing the samples and forms are transferred daily to the central NBS lab in Tel HaShomer Hospital. This transfer is carried out by a dedicated courier service that operates over all national territory at the expense of the Center.

Every newborn is immediately registered in the hospital and within 24 hours after birth acquires a national identity number (ID). Israeli babies receive the ID that will accompany them for life (similar to the Italian "codice fiscale"). Neonates whose citizenship status is unclear (e.g. born to a tourist) receive a temporary ID that will be replaced later according to personal status.

The computer handling the demographics in each hospital is programmed to transmit the data on newborns to the NBS Center's computer. By cross-checking the cards against the e-data, the Center makes sure that each child's blood spot collected at birth arrives to its lab. The Center makes a further confirmation of the ID written on the blood spot card by checking it electronically with the Ministry of Interior Affairs, where the baby's registration in the hospital is ultimately approved a few days later by the government's officials. Children born out of

hospital (e.g. home birth) are brought to the local office of the Ministry of the Interior Affairs for the sake of registration within a week.

It follows that the NBS Center has three sources of information regarding every neonate – 1. The cards accompanied by the dedicated forms; 2. The hospital data system and 3. The Ministry of the Interior Affairs (the national census). As a policy, the Center cross checks all three sources in order to make sure that every born baby has been screened (or an appropriate refusal process has taken place).

Parents have the possibility of opting-out from newborn screening. In case they express such refusal, the health care team has the duty to inform them in detail about the risks such a refusal entails for the health of their baby. In case parents persist in their position, they have to sign a dedicated form of informed refusal, where it is specifically said that they relieve the hospital from the responsibility of not screening the child. In 2010, 138 families have signed such an informed-dissent paper. Empty Guthrie cards accompanied by the refusal forms are sent to the Center along with the ordinary screening samples. The law does not prohibit the Center's personnel to contact the refusing parents later on.

Many of the refusals are temporary. In case parents sign an early discharge form and take the baby home prior to 48 hours, they are asked to sign the refusal form and come back for screening after 48 hours. Alternatively, screening is possible also in the local Drop of Milk clinic. When the baby is screened and his or her screening package arrives, the refusal information is shelved away, outside the data system.

Once the screening packages (the Guthrie cards and the forms) have arrived in the central lab, the barcode is read and is compared with the ID electronically sent. Then, the Center

confirms the reception of the mail, the number and the identity of the blood spots to the hospital where they originated.

According to the last Ordinance of the Ministry of Health, the dedicated forms contain two clinical items of information. First, information on “suspicion of a screened disease”, which the hospital team is expected to know through ordinary patient anamnesis of the mother (6.15), and, second, technical information such as whether the child is premature (less than 36 weeks of pregnancy) and whether this is the first or second sample (second sample following unclear results in the first one). Additionally, the Center’s computer is programmed to retrieve from the hospital the weight at birth as well as gestational age, and incorporate these data in the algorithm calculating the normal threshold of abnormal results. In this way, the rate of false positive is low relative to other NBS programs (see CAH results).

Results of the analysis are daily reported back to the hospitals. Negative results are also uploaded onto the webpage of the Ministry of Health for the parents. In fact, in most cases, after a few days from birth, parents can access the web page of the Ministry of Health, Public Services, Department of Genetics (<http://www.health.gov.il/yelod/default.aspx>) where they can find the test results of their baby, upon typing the mother’s and the baby’s IDs. Ambiguous and positive results are never uploaded. In this case, the message that appear on the web instead is an instruction to contact a doctor.

The following image is an example about how negative test results appear in the webpage of the Ministry of Health, after parents open the NBS data of their baby by crossing the mother’s ID and the ID of her baby.

Ministry of Health

Newborn Screening Lab

Results of lab testing.

Surname : [mother' surname]

Baby's date of birth:

The screening tests that have been performed resulted with the normal range.

[List of diseases, in English]

These tests do not rule out these diseases hundred percent; they do not rule out other conditions either.

In any case of suspicion, one has to consult the caring physician and perform the tests s/he advises.



משרד הבריאות - מדינת ישראל

המעבדה לבדיקות סקר ביולודים

תוצאות בדיקות מעבדה

שם משפחה	בחסה
218123180	מספר תעודת הזהות של היילוד
14/03/2009	תאריך הלידה של היילוד

בדיקות הסקר שבוצעו נמצאו בתחום הנורמה -תוצאות תקינות

- ◆ Phenylketonuria
- ◆ Congenital Hypothyroidism (primary)
- ◆ Congenital Adrenal Hyperplasia -21 hydroxylase deficiency
- ◆ Maple Syrup Urine Disease (MSUD)
- ◆ Homocystinuria
- ◆ Tyrosinaemia type 1
- ◆ Glutaric Aciduria type 1
- ◆ Methylmalonic Acidaemia
- ◆ Propionic Acidaemia
- ◆ Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)
- ◆ Very Long -Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)

בדיקות אלה אינן שוללות קיומן של מחלות אלה במאת האחוזים ו/או מחלות מולדות אחרות. לכן, בכל מקרה של חשד למחלה על הרופא המטפל להסתמך על ממצאים קליניים ולבצע בדיקות אבחנתיות.

תאריך : 19/11/2011יש לצרף עותק זה לתיק הרפואי של הילד

In case of suspicious results, retesting the blood sample is performed, either biochemically or genetically, depending on the specific condition. If the quality of the samples appears inadequate or, for other reasons, resampling seems necessary, either the hospital receives a notice (in case the baby is still in the hospital, which is common occurrence with problematic

results) or the Center contacts the parents directly. This is also the procedure when results are clearly abnormal.

In Israel, genetic information may be communicated to patients by either licensed physicians or licensed “genetic counselors”. These standards have been kept also for those people working at the NBS Center and interacting with the parents of children with positive results.

Since its opening in 2007, the head of the NBS Center has a PhD in genetics, and is also licensed as a genetic counselor. In the Center there is one more genetic counselor, an RN. They are the only two persons who directly contact parents. In addition to these two people, only one more person has full access to the lab’s data – the head of the lab. These three people work together as a team located in one place, thus helping information exchange and follow up of the process.

In case the Center wishes to contact the parents, it first uses the contact information written on the dedicated forms, which contain a specific question regarding a telephone number in the place where the baby and mother are expected to stay in the first two weeks after discharge. If this is not satisfactory, the Center may use the demographic and contact data that appear on the hospital records of the mother. They are usually synchronized with the database of the National Security Agency and the Medical Insurance Provider. The Center may also contact directly the Ministry of the Interior Affairs. In the few rare cases that parents are not located, the Center may contact the local Drop of Milk Clinic and the local office of public health. The latter has the legal power and means to search for a “lost” child. The ultimate goal is to get one of the parents (or guardian) in contact with the Center’s counselor and/or to bring the child to a hospital where the local counselor may talk with the responsible physician.

Whoever answers the telephone (father or mother) is first identified as one of the parent of the child. No conversation occurs with other people of the family. Then, she or he is briefly asked to bring the baby for a check-up in the emergency department of one of the hospitals that has a genetic clinic in cooperation with the Center. A telephone number is given, in case of further questions (usually, the personal cellphone of the genetic counselor calling from the Center). The Center's policy is never to disclose any details regarding a particular suspicion other than the communication of a suspicion of some metabolic malady. At any rate, a definite diagnosis is always communicated by a doctor specialized in either endocrine or metabolic diseases, in one of the clinics affiliated with the program and in a face-to-face doctor-patient meeting.

Overall, the Center makes at least three phone calls. The first is to the child's parents or guardians; the second is to the emergency department doctor that will expect the arrival of the child; and the third is to the local endocrine or metabolic specialist. It is noteworthy that one of the conditions for recognition of a clinic as affiliated with the NBS program is the 24/7 on-call availability of such an expert (12.2). Interestingly, although expertise in clinical genetics exists in Israel, the Ordinance shows a practical orientation, directing the children to experts that could handle their clinical problem immediately.

Once the child is brought to the hospital, definite evaluation and diagnosis are made by the local experts, usually in cooperation with the Center. Later on, the local clinic reports back to the Center the final diagnosis. In this manner from the moment of blood sampling until either clearance or diagnosis, every neonate in Israel is monitored by the Center. This may be defined as the initial phase of the screening – from entry into the system until clearance or transfer of responsibility to a local expert is achieved.

By telephone exchanges, the Center makes sure that the baby has arrived at the specific health care institution and is retested. In case the child is not brought for retesting, the Center activates all its resources and contacts in order to understand the issue and to overcome it. So far, no family has refused to bring the baby for retesting, but practical problems may emerge. An example is lack of means of communication or means of transportation; another example is problems at home due to which some poor mothers wouldn't travel for medical testing of an apparently healthy baby. Cultural barriers may operate too. An example of this is the need of the husband to be free from work in order to drive mother and baby to the hospital. Some Muslim women do not travel unaccompanied at all. These and other challenges are usually handled by local capillary networks, mainly based on local "Drop of Milk" clinics, where, typically, the healthcare team is local, well versed with the local culture and familiar with the people around. Additionally, every "Drop of Milk" clinic has one nurse entrusted with responsibility over NBS issues that may arise, from patient education to communication with the Center.

The directives to nurses regarding NBS screening request that efforts be made to have the baby screened up to 4 months of age. This clause is usually relevant for Israeli babies that are born abroad and whose screening status is unknown.

Representation of the last official report on NBS results (May 2012)

The expanded NBS program is fully active from 2009. Officially, expanded NBS program screens for the following diseases:

PKU – Phenylketonuria

CH – Congenital Hypothyroidism (primary)

CAH – Congenital Adrenal Hyperplasia

MSUD – Maple Syrup Urine Disease

HCY – Homocystinuria

TYR-1 – Tyrosinaemia type 1

GA-1 – Glutaric Aciduria type 1

MUT – Methylmalonic Acidemia

PROP – Propionic Acidemia

MCAD – Medium Chain Acyl-CoA Dehydrogenase deficiency

VLCAD – Very Long Chain Acyl-CoA Dehydrogenase deficiency

Other diseases are included as pilot in the official program, which may vary according to results.

The last Center's official report was issued in May 2012⁹. This report covers NBS data during a period of three years, from 2009-2011. In these 3 years there were 506,759 newborns overall.

The diseases that have been found out are:

268 cases of hypothyroidism (1: 1900)

25 cases of congenital adrenal hyperplasia (1: 20,000)

⁹ Available at http://www.health.gov.il/PublicationsFiles/newborn_2012.pdf

92 cases of severe metabolic conditions, including PKU, which requires immediate treatment (1: 5,500)

Overall, 385 cases were of severe diseases. In most of the cases, early diagnosis facilitated the prevention of serious disease's manifestations.

From 2011, due to a dedicated web connections among different offices, as described in the previous part, it became possible to verify that all neonates are tested in due time, as well as to know who is not tested. For example, in the year 2011, out of 170,000 newborns, 170 children were not tested due to parental refusal (1:1000). The program is technically operative from June 1st 2008 on 11 conditions, but only from 2009, the program turned from being a pilot to being official.

The following table shows the results of Congenital Adrenal Hyperplasia.

CAH	2008 ¹⁰	2009	2010	2011
Sick children	7	8	11	6
Salt losing variant (severe form of the disease)	6	8	7	3
False positive requiring retesting	27	51	42	36
False positive after second testing	2	2	1	0

In this pathology, the low rate of false positive is attributed to the incorporation of birth-weight and week of gestation of the baby into the algorithm of the computer system.

¹⁰ For CAH only, pilot began already in 2007.

Congenital Hypothyroidism was one of the conditions tested before the expansion of the NBS program. The number of sick children is relatively high, but also false positive results were an issue, with a rate of 0.73%.

CH	2008 ¹¹	2009	2010	2011
Sick children	69	59	96	113

In 2011, the threshold of the cut offs were changed, and the rate of false-positive fell by 50%, without missing a single case of true hypothyroidism.

Conditions diagnosed by MS/MS.

The following table shows the number of patients detected by MS/MS and afflicted by severe conditions.

Condition	2009	2010	2011	TOTAL
PKU	6	10	5	21
MCAD	6	1	4	11
VLCAD	3	3	1	7
MSUD	1	3	2	6
GA-1	3	1	1	5
HCY	1	0	1	2
MUT	1	1	0	2
PROP	3	0	0	3

¹¹ It was already tested before the expansion.

Tyr-1	1	1	0	2
TOTAL	25	20	14	59

Patients afflicted by other serious conditions.

Condition	2009	2010	2011	TOTAL
Isovaleric acidemia	4	0	2	6
Hypermetioninemia	6	1	0	7
Tyr-2	1	1	1	3
Etimalonic encephalopathy	0	2	2	4
GA-2	3	1	1	5
Citrullinemia	2	0	0	2
Long Chain Acyl-CoA Dehydrogenase deficiency	0	2	0	2
CPT-2	0	2	1	3
Carnitine/acylcarnitine translocase deficiency	0	2	1	3
TOTAL	14	10	9	33

Other conditions detected.

Condition	2009	2010	2011	TOTAL
3-methylcrotonyl-CoA Carboxylase Deficiency 3MCC	-	9	6	
Maternal 3MCC deficiency	-	7	7	
2-methylbutyryl-CoA dehydrogenase deficiency	1	0	0	1

Hyper phenylalaninemia	12	14	26	52
Maternal PKU	0	0	1	1
Tyrosinemia transient	32	50	10	92

Following a discussion in the Israeli society of metabolic disease, the committee responsible for NBS concluded that 3MCC is not a disease or a condition of any clinical significance, and therefore decided to remove it from the program.

Comments on the NBS test results

This report summarizes the impact on severe and treatable conditions, which summed up to 385 children out of half a million. Put in other words, the NBS service “saved” 0.077% (1:1300 live births).

With this data in hand we also calculated the false positive rate. Calculation is carried out according to 2011 standards of normalcy, extrapolated to a population of half a million neonates. We may observe that nearly 90% of the “false positive” cases are due to suspected hypothyroidism ($0.74\% \times 0.5 \times 500,000 = 1850$).

Other “false positive” children are 142 related to tyrosine metabolism (hyperphenylalaninemia + transient hypertyrosinemia) and 5 related to CAH testing.

It may be commented that the problem of proper use of thyroid related tests is a well-known problem in clinical medicine, and it is not unique to NBS. The appropriate indications for testing and interpretation are debated even in the context of clinical care and “screening” of adults who are sent for “routine” check-ups.

We have also calculated the overall number of reported conditions whose clinical significance is unclear (so called “secondary conditions”). They sum up to 33 out of 500,000 babies tested.

In sum, it may be observed that the challenge of false positivity and “patients in waiting” is almost exclusive to thyroid related screening. Since screening for hypothyroidism is considered “life-saving”, and since it belongs to the pre-expansion era, it seems that the bioethical discourse on “false positive” screening is unrelated to the expanded NBS.

It may also be observed that although the Israeli program tests for “only” eleven core conditions, sixteen other secondary conditions were detected and reported. From a patient’s perspective it may be said that the Israeli NBS screens for 27 conditions.

None the less, one cannot describe the Israeli program as blindly expansionary, since two conditions (3-methylcrotonyl-CoA Carboxylase Deficiency and Maternal 3MCC deficiency), which are still part of the panels of most USA states, have been removed from the Israeli program.

Official data regarding the penetration of the program in 2011

Live neonates by the census of the state (ministry of interior)	170,982
Number of Guthrie Cards sent	170,393
Neonates without card (mostly dead)	589
Percentage of neonates without citizenship or any other resident status (tourists and illegals)	3.3%
Percentage of neonates whose cards are accompanied by e-data from the hospital	98.2%

Number of first screening test	170.225
Number of unscreened babies	170
Number of unscreened babies with refusal forms	127
Unscreened and considered “lost” to the system	43
Overall non screening rate	1:1.000

False positive data

Requests for retesting due to suspicion of hypothyroidism	0.35%
Requests for retesting due to technical reasons	1.25%
Overall retesting rate	2%

The vast majority of request for retesting due to technical reasons is in relation to still hospitalized babies who suffer from prematurity and other significant illnesses.

The official report does not separate this group of children for whom retesting has minor impact on the parents from apparently healthy neonates whose parents receive a phone call with requests for retesting. Such information was presented by the Center’s director in March 2011, during a conference in Tel Aviv Medical Center. The data is from January 2011, reflecting a sample of one month. The following table shows the retesting requests during the period of January 2011 on 14482 newborns.

Recall	NICU	home	%
CHT	25	20	0.31%
CAH	2	2	0.03 %
Phe	3	0	0.02 %

Tyr	3	0	0.02 %
AA	3	0	0.02 %
OA	3	2	0.03 %
FA	2	6	0.06 %
Total			0.49 %

The following table shows how many of the recalled children were referred to a specialist.

Referrals	NICU	home	%
CHT	8	14	0.15%
CAH	0	0	
Phe	0	2 hyper Phe	
AA	0	MSUD	
OA	0	4 -3MCC	2 isolated 2 maternal
FA	0	MCAD	
Total			0.20%

In this sample 0.5% (1/200) of neonates was re-tested (initial test yielded borderline values or was technically flawed), while only 0.2% were referred to a dedicated specialist with a clearly abnormal screening results. Since the average true positive rate of NBS is 0.1%, it seems that half of referred children were ultimately sent home as healthy.

In the same conference, data on ethnicity was represented. It may be noted that in Israel ethnicity and religious group do not overlap (for example, there Arabs are not only Muslims but also Christians). Nonetheless, the following table shows the high incidence of metabolic and genetic diseases among Muslim population, the highest incidence of all being among the Bedouin group. The data are relative to the period from May 2008 to January 2011, when 472,947 babies were born overall.

Ethnic / religious group	% newborn	% patients
Jews	72.35	42
Muslims (Arabs and Bedouin)	21.45	56
Druze	1.61	1.8
Christian	1.27	0.9

Another significant item in the program is the timing of arrival of the blood samples. The following table shows how many days it takes for the Guthrie cards to arrive to the central laboratory.

Up to 5 days	45%
On the 5 th day	22.3%
Up to 7 days	2.3%
After 7 days	30.4%

Affiliated centers

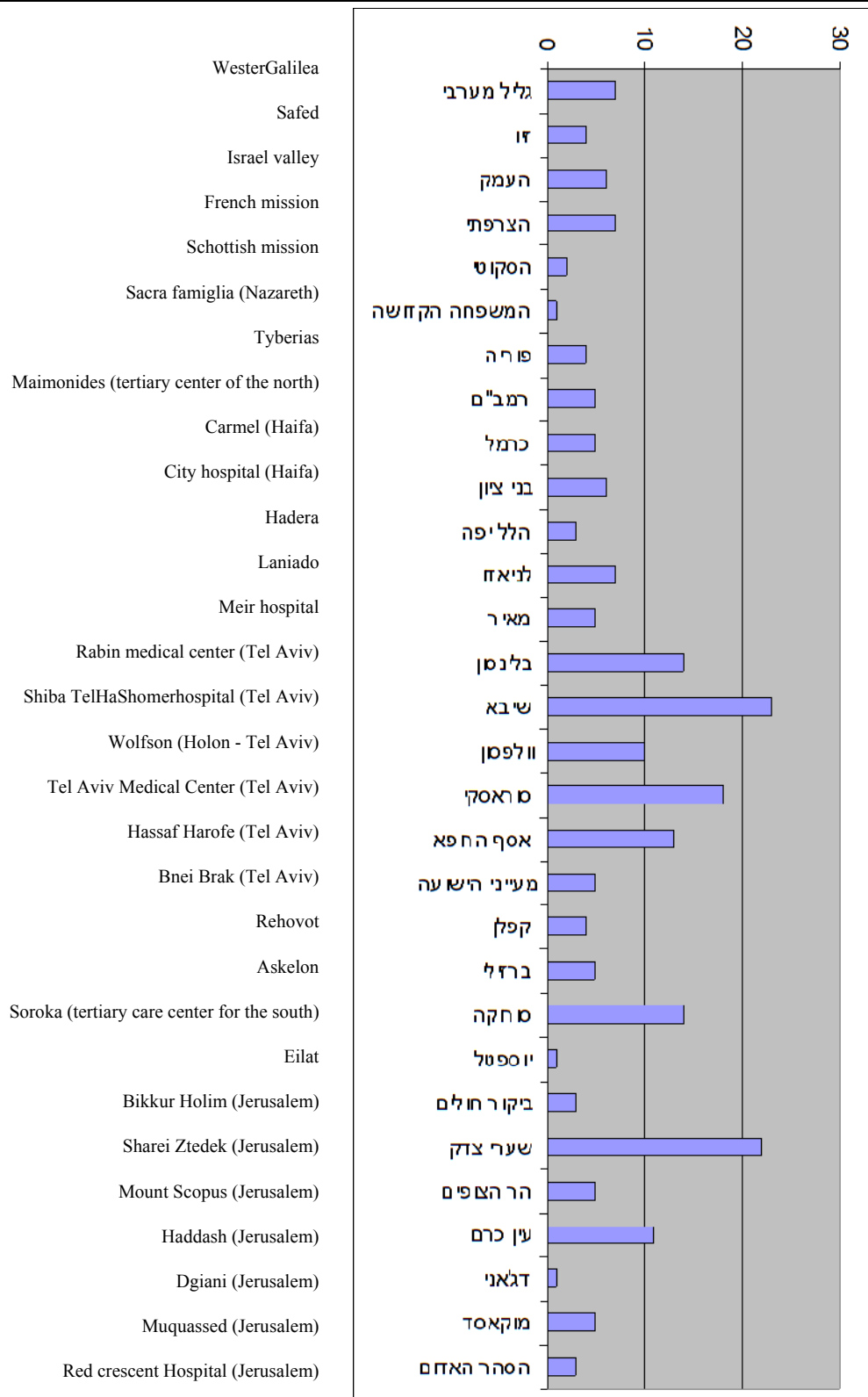
When the expanded NBS program was drafted, worries were expressed that the centralization of NBS might lead to the centralization of care for metabolic and rare diseases. Such a development was not in line with governmental policy of peripheralization of medical excellence and with the habit of local pediatric healthcare. Moreover, although carried out in hospitals, Israeli NBS was already considered integral to the state's direct responsibility for baby care in the tradition of "Drop of Milk" clinics. Hence, the NBS program was left as part of the Department of Community Genetics in the Ministry of Health, while final diagnosis as well as follow-up was open to local clinics, however small. The Ordinance of the Ministry of Health posited entry criteria for recognition (i.e. the on-call availability of 24/7 expert in either endocrinology or metabolism). Following these criteria, thirty hospitals have registered as recognized Centers of Referral. This policy clearly gives priority to local care and to the development of high end local clinics, but, at the expense of the volume of practice that is usually expected of genuine tertiary care services. One exception is the national PKU clinic, already operative in Tel HaShomer before the expansion of the screening program, which kept following all children that suffer from all forms of hyper-phenylalaninemia.

As we can see in the following table, actually all hospitals in Israel are registered. The table, that lists the hospitals by geographic area, from the North to the South of the country, also shows the number of patients per center.

As last remark, it may be noted that no structured feedback mechanism on "false-negatives" results exists. The affiliated centers are in constant contact with the Center, but they do not have a structure of reporting children who are diagnosed clinically despite negative screening results. It is unclear whether such cases occur at all. What we know is about the case of one baby born in 2012 that could have been saved by screening, which his parents had refused.

In the next page we find a list of all Israeli hospitals where childbirth takes place (Currently there are not active birth centers in Israel). The list is ordered from north to south. The columns (set horizontally in this table) indicate the number of children who screened true-positive during one year. All of these hospitals are also recognized as screening centers (see next table). This results in decentralization of care and data, as well as in increased competition among local clinics for “interesting” cases and the money associated with the follow up of these children. It also poses formidable obstacles on any research targeted at specific groups of children (e.g. those diagnosed with one particular condition, or “false-positive” cases).

Hospitals recognized as screening centers, with number of cases referred to in one year



CHAPTER FIVE: COMMUNICATION AND INFORMATION IN THE ISRAELI PROGRAM

Informing patients

Information is a key element in the relationship between health care professionals and their patients. In fact, with the exception of certain situations where consent to care is presumed, such as in emergencies, information about diagnostic procedures and treatment is prerequisite to the provision of professional, legal and ethical care. When the patient cannot give informed consent, others do it – it is the consent by a fully informed proxy. Information and consent are two interwoven aspects within and along the process of care.

In medicine, information, as well as consent, is not a "one for all" event. Instead, it can be described as a flow of communication, which is why we usually talk about the "information process". Within it, we find moments that are more salient than others depending on the level of awareness that patients acquire in relations to the subject at stake, including their ultimate expression of their acceptance or refusal of a particular health care procedure.

In our case, we wish to explore the information process related to NBS. More specifically, we wish to see what are the resources of information and strategies of communication adopted by the health care system in order to raise awareness of the theme in the target population of NBS – parents, and especially, pregnant mothers – about this public health preventive program.

Because NBS is governed as a public health program, we may differentiate the information provided by the health care system to the public by degrees of specification:

1. Information that is generally transmitted to or is generally known by “the public”.

2. Information that is more specifically construed in order to target a specific group – pregnant women, for example;

3. Information that is specifically transmitted to parents whose child has been fished out by the NBS, and that may become a "real patient", if the first positive result is confirmed.

These different degrees of specification are borne out by the different levels of formalization – from more legally binding directives to less formal and more personally transmitted. Therefore, we may distinguish:

a. A formal level of information – it is about how the law, including case law, determines the way information should be constructed, how its mode of communication should be, and who are the agents responsible for it.

b. A quasi-formal level of information – it is about the official or professional publications aimed at either the public or the persons giving consent. These publications bear no legal power; however, as documents produced and disseminated by the government (or other responsible bodies), they set standards.

c. The actual art of doctor-patient communication, the oral and intimate events that take place in connection to a specific health problem or personal request. In Israel, this happens mainly in two occasions – when parents express their wish to refuse NBS; or when suspect results are found and a specific request to retest the baby is transmitted to parents.

Jewish and Israeli culture: relevant considerations

Even though no systematic survey about the knowledge on NBS by the Israeli public has been published, it seems that the average parent is aware of the procedure. This observation is supported by numerous personal conversations with ordinary people as well as with healthcare professionals who discuss their own experience. This situation may be accounted for by historical and cultural reasons.

From a historical perspective, NBS began quite early, during the 1960s. When Israel was among the first nations to adopt a NBS program, it was quite poor and small. However, it had had a very strong system of children-oriented public health, which had originated in the young country's response to the waves of Jewish immigration throughout the 1950s. Most of these immigrants came from undeveloped countries with rudimentary healthcare services and high rates of infant mortality. Whereas owing to lack of public resources, hundreds of thousands of these immigrants were housed in temporary shelters and tents, the state concentrated efforts on health education and public health. Strong incentives were created in order to make women give birth in hospitals and dedicated birthing centers, and bring their children to routine check-ups that included vaccinations and other preventive and health promoting measures. Even illiterate mothers became fast aware of the routines and the cultural expectations to abide by them. In the 1960s almost all of these temporary camps had closed down and people had moved to new housing projects. The emergent American practice of NBS was aimed at very rare condition, not a perennial health risks such as open sewage and polio. However, the early adoption of NBS by the Israel healthcare system appeared a natural step by a highly efficient pediatric healthcare system. Despite significant health gaps and disparities in access to healthcare, the Israeli government invested significant efforts in an egalitarian basic healthcare for babies and young children. Whereas no national healthcare system existed at the time, national standards for baby

care did exist. In this spirit, when NBS was introduced, it was initiated as a national program and not as a pilot service limited to a certain region or population. This brought forth a need to locally tend to children with positive screening results, as well as worried parents to children in the family or neighborhood. The outcome was the creation of a local and dispersed network of post-screening care and follow-up of diagnosed babies. Virtually every hospital had at least one professional dedicated to what we now refer to as genetic or metabolic diseases of childhood.

This situation hitched well to Jewish culture, because awareness of the possibility of familial conditions is central to the matchmaking mentality of the traditional communities. The Talmud and other formative religious texts underscore parental duty to protect and promote their children's health. Most of the Talmudic advice is medically arcane, but people's awareness of their personal responsibility for the health of their children is strong. Contemporary demographers and historians attribute the relative low infant mortality in the pre-modern Jewish communities to the pro-active attitude to children's health relative to the non-Jewish tendency to fatalistic acceptance of God's will (Derosas 2003). Some Jewish preventive measures were clearly spiritualist; but others were secular, as the Talmudic law encouraged people to embrace every reliable and advanced method that is likely to improve children's health.

Additionally, the Jewish Diaspora created distinct and remote communities, which on one hand shared Jewish religion and culture, but on the other, owing to the small size and isolation of many communities, developed distinct patterns of genetic diseases (see appendix 6). Today, the descendants of virtually every Jewish community suffer from typical patterns of genetic diseases. For example, the Ashkenazi (European) Jews tend to have high rates of Tay Sachs and Lesch Nyhan, Jewish originating in the Mediterranean basin are prone to Thalassemia and the like. First, for centuries people became aware of these patterns and of their implications on marriage.

But when Jewish immigrants came to Israel from all over the diaspora, Israeli medicine found itself facing an unprecedented variety of genetic conditions. This unique situation, along with the high scientific level of Israeli medicine, contributed to the thriving of Israeli genetics both as a science and clinical practice. Put in other words, the concentration of very diverse genetic backgrounds, the cultural awareness of responsibility to prevent children's diseases, and the scientific ambitions of the secular medical establishment, backed by state support of universal and high quality pediatric public health, combined together to produce the special ambience that was friendly to NBS and capable of handling treatment of diagnosed children. Because of this special combination of factors also included grass-root and religion based practices and beliefs, many – perhaps most – people became aware of NBS (as well as of the importance of boiled water and vaccination) much before they had proper houses and stable jobs. When Israel adopted a national healthcare service in 1995, pre-conception genetic testing were offered for free to every resident, each deserving to be tested for the genetic conditions typical of his or her community background. These tests are very popular, and discussed with family doctors and gynecologists. Many observant (i.e. Orthodox) Jews prefer to test before a decision on marriage. Almost every secular woman is advised by her gynecologist to be tested when she discusses her intention to get pregnant. A landmark Supreme Court ruling from 1982 (Supreme Court of Israel 518/82 Zeitsov v. Katz) found a geneticist negligent and responsible for “wrongful life”. In this particular case, a woman with a severe neurological disease (Hunter's disease) running in the family approached a geneticist asking her whether it would be safe for her to get married and have children. The geneticist, who wrongly told her that there was no risk involved, argued in court that the ultimate responsibility for having children is the parents', but this line of reasoning was not accepted and the geneticist was found guilty. By this ruling Israel was also among the

first countries to recognize the legal entity of “wrongful life”. Soon after, law suits were directed at physicians who failed to alert people, even those who did not ask either about either genetic or other kinds of risk to their unborn or future children. The overall impact of this development was high awareness of parental and professional responsibility for the prevention or early detection of serious conditions in the child. Even though no similar legal proceedings have been associated with NBS in Israel, it is reasonable to believe that awareness of NBS did not fall short of the standard practice regarding children’s health. Because they object to abortion, some Hasidic groups object to prenatal screening tests, and some rabbis advise pregnant women to ignore doctor’s advice to abort. However, such considerations are irrelevant when NBS is at stake. This is borne out by the rabbinic tendency to respect “the way of the world”, which means that the local standards of safety and care bear religious value as well. Hence, once the state institutes a public health program such as NBS, the rabbis would endorse participation as a religious duty.

The concept of “technology assessment” is alien to Jewish law and mentality. So long as the government, even if non-Jewish or secular, acts in good faith, the rabbis respect the lay standards of precaution, and deem their negligence as violatory of the Jewish religious duty to protect life (Steinberg 1996, 397-398). Even though Israel is a secular state, the religious groups exercise considerable political power. Besides, the healthcare authorities strive to program services in harmony with religious and cultural values. Whenever a potential conflict with religious law arises, such as often occurs in the context of infertility and transplantation medicine, rabbinic participation in the regulative process is sought. However, because the expansion of NBS in Israel was done by a purely professional body and nobody saw any potential conflict with religious values, no rabbinic voices have been heard in relation to the ethical and legal aspects of NBS. It is not unlikely that awareness of NBS among religious

women is much higher than among the learned rabbis. However, the unquestionable awareness of NBS does not necessarily entails awareness of its expanded format. This might be merely a matter of time (expansion took place only six years ago), but it might also reflect the ever growing complexity of prenatal and postnatal care and health-related information. Indeed, the expansion of NBS (but not the pre-expansion program) has been accompanied by a dedicated body of secondary legislation that specifically refers to the duty to inform prospective mothers.

The secular Zionist ethos envisioned the State of Israel as a shelter for the Jewish people, protecting them from persecution, discrimination and other adversities of the diaspora. Zionism also envisions a rehabilitation of a healthy and strong nation. Israel's perpetual preparedness to war in terms of centralized mobilization of resources is also borne out by the efficient coordination and commitment of diverse organs of the state (public health officials, primary care, ministry of the interior, information technologies, police etc.) to assist in the tracing of every unscreened or positively screened baby, no matter how difficult the task (e.g. illegal immigrants, nomads living in tents or recalcitrant and reclusive lifestyles).

A striking example to this mentality is the incorporation of neonatal care equipment in Israel's portable military hospital that is dedicated also to disaster medicine. As far as we know, Israel is the only country that carries with obstetric and neonatal equipment in its disaster missions (Barilan, Brusa and Halpern 2014).

The formal structure of information-giving

The official ordinance (17/2009) dedicates a whole chapter to “information to the pregnant woman”, instructing the physician who follows the pregnancy to “explain to the woman the screening tests and their significance”, to hand her the ministry of health's brochure related to it

and to document this process in the chart. In case the woman has chosen to give birth at home, the doctor should ask her to sign a special form indicating her awareness of the screening tests and responsibility for them.

This formalization of the information giving process regarding NBS is exceptional. Although communication with patients, informing and educating them about health are central constituents of medical care, these issues have not been governed directly, but conducted by professional standards and the informal art of “professional care”. Certain standards have been set by case law, when the courts, especially the Israeli Supreme Court, ruled certain conduct of information giving as negligent (e.g. failure to inform the patient that surgery will be performed by a doctor in training). The first official directive regarding patient information appeared in the Israeli law in the context of terminal illness. The Patient Nearing Death Act (2005) requires that every patient with a prognosis shorter than six months be informed about this grim situation and be asked about the kind of treatment he or she might wish to have. Precisely because treatment decisions at the end of life are subjected to personal values, the law expects of doctors to actively find out the wishes of their patients. However, a law on information giving with regard to an ordinary and default practice, such as NBS is noteworthy. It is unclear whether it reflects a particular sensitivity regarding NBS or a novel trend regarding the legal codification of information in Israeli biomedical law.

The codification of information in the NBS ordinance is especially striking in light of the first primary legislation in Israel that prescribes information-giving in the context of medical care – The 2000 Genetic Information Act. According to the law, any “genetic testing” must be conducted by a specifically licensed genetic lab (clause 3); the informed consent to testing must cover information about the potential implications of such testing, including information about

family members (clause 10). Counseling with regard to the results of “genetic tests” should be given by healthcare professionals licensed in “genetic counseling” (This excludes expert physicians whose expertise does not cover genetic counseling). Genetic testing of minors depends on the informed consent of the parents/guardian and a “reasonable clinical judgment” that the results of such a test are likely to benefit the child (clause 25). The law does not require genetic counseling prior to testing, but, for example, the directive of the Ministry of Health on genetic testing in the context of early detection of cancer (General Director’s Directive 10/12) specifically requires that patients receive such counseling prior to testing.

Technically speaking, all of this is irrelevant to NBS, simply because the 2000 Genetic Information Law defines “genetic testing” as tests aimed at DNA analysis. But, evidently, it does not matter whether one learns about a mutation by a direct genetic test or indirectly, by means of biochemical markers. Indeed the deployment of MS/MS technology in the context of NBS produces information about genetic diseases, and often about carrier status as well. Today it is a common practice to confirm positive NBS results by means of DNA analysis, a practice that is illegal in Israel without informed consent. Such practice is not mentioned in the directive, law or educative material. Because the Israeli law on genetic information was enacted when expanded NBS was not on the Israeli horizons, an amended law, with a chapter dedicated to NBS, is under deliberation in the parliament for over two years.

The proposed amendment changes the definition of “genetic testing” from DNA analysis to “analysis of biological material that yields genetic information”. This significantly expands the ambit of legal protection of genetic data. The proposed chapter on NBS authorizes NBS testing without informed consent, and without distinction between biochemical and genetic analysis. This is the only exception proposed to the primacy of informed consent to genetic

testing. Whereas the proposed amendment broadens the ambit of the law, it also diminishes the power of individual parents in relation to NBS of their children. The ongoing debate in the parliament brings into light the complexities of categorization and naming.

In parallel to the dissemination of the information brochure to birthing mothers, the department of community genetics issued an educational booklet aimed at the healthcare team (undated), titled, early detection of diseases in healthy neonates: newborn screening. The booklet set the American College of Genetics' guidelines as its professional source. The criteria for screening are three – 1. Serious diseases, 2. Relatively frequent and for which 3. An effective treatment exists when administered prior to the appearance of symptoms. Interestingly, other criteria from Wilson and Jungner's, such as "acceptable by the public" are not mentioned. Even though the incidence of some screened conditions is in the range of one to hundreds of thousands, there is no explanation regarding the notion of "relative frequency".

After dedicating two pages to an overview of the program and its general philosophy, one page is titled, "The importance of informing parents":

In order to inform every birthing woman that NBS is performed post-natally, and in order to make sure that she understands the purpose of the tests, it is necessary to inform her already while pregnant. In addition to the handling of the brochure [=the informative brochure written for expecting mothers, discussed in the next section], it is desirable to discuss NBS with her, highlighting the following points:

- The affected babies appear healthy and diagnosis [of their metabolic disease] is impossible by means of ordinary medical testing.
- Most affected children have no familial story [of such diseases].

- In case the condition is diagnosed early, it is possible to prevent serious complications such as mental retardation.
- The test involves the sampling of a few drops of blood from the baby's heel, prior to discharge.
- It might be necessary to contact the family in the days after discharge, because retesting or further testing might be necessary. Hence, it is imperative that the hospital team have telephone numbers and other means to contact the mother in the post-discharge period.
- The ministry of health recommends the testing of every neonate. However, the parents have the opportunity to refuse it. The parents [who wish to refuse] must be aware of the implications of such a choice. Should they refuse, they have to contact a neonatologist after birth and [ask for] the refusal form.

The next seven pages are dedicated to the techniques of sampling and handling of the relevant bureaucracy. The last seven pages contain information on the diseases screened. Incidence rates are given on PKU (1:10,000-1:15,000), hypothyroidism (1:3000) and CAH (1:10,000-1:15,000), but not on the ten "additional metabolic conditions" screened. Even the healthcare team is not informed that their incidence is ten to a hundred times lower than the leading three conditions. More interesting, from our point of view, is lack of any information to professionals about the manner of information giving to prospective mothers. Is the gynecologists expected – by either legal or mere professional standards – to tell the pregnant patient that NBS is a "genetic testing" of her baby? In a culture that grants "genetics

information” such as high status of moral saliency, the inclusion and exclusion of reference to the nature of the testing is of much significance.

Returning to the directives on NBS, they do not contain any instructions regarding the information of birthing mothers when NBS actually takes place. The directives merely state that mothers who refuse screening, need be informed and made to sign a special refusal form (2009 directive, clause 4.2).

Accounting for this structuring of information is not straightforward. On one hand, it seems that informing pregnant woman about NBS is psychologically superior to approaching women who give birth, adding a whole lot of complex information to their already highly intense emotional and physiological experience. Early information allows time and energies for further study of the subject and for the consolidation of a properly informed opinion. On the other hand, however, according to the common understanding of the doctrine of informed consent, the professional responsible for patient information is the one responsible for the procedure in question. It is especially striking that the duty to inform about a pediatric procedure is placed on the shoulders of gynecologists. Indeed, they have plenty of experience in advising woman on various health risks to their coming children, and yet, they have no experience whatsoever in counseling about the meaning of baby’s tests results, the nature of these tests and the kind of follow up that might be needed.

We may observe that the gynecologists’ role is actually best understood in terms of patient education, rather than clinical consultation, which takes into account the particularities of the situation. In a similar vein, a gynecologist may explain about the possibility of cesarean section to a pregnant woman, but only when the cesarean section becomes a real and close option, informed consent becomes relevant. One might say that cesarean section is a far away

option that not all women go through, and therefore the informed consent is necessary only in case the procedure is performed. Instead, NBS is a "universal" procedure that is offered to everybody and therefore is done by default, and regardless of the clinical circumstances, thus rendering a personalized process of informed consent unnecessary. As a matter of fact, there is no information to add. However, it is difficult to stand by this line of reasoning because other uniform procedures, such as vaccination, do involve personal informed consent upon administration. Moreover, whereas parents typically bring their children to the clinic for vaccination, women check themselves into hospitals in order to give birth, not necessarily being aware, or even desirous of NBS.

It seems reasonable to suppose that patient education, about NBS, for example, primes the patient for making a conscientious choice in real time, even in stressful circumstances. It is much less reasonable to forgo the need for an actual event of informed consent, especially when the intervention in question is value laden and under debate. However, we must keep in mind that the nurse that obtains a few drops of blood from the neonate does not actually perform the "procedure". They cannot be compared to surgeons who inform their patients prior to surgery. Missing still is an instrument that guarantees awareness of the saliency of the procedure at the time of performance.

This is a crucial issue. In clinical medicine and medical research, consent "in real time" is essential. Patients must consent to surgery, experimentation, blood donation and other procedures when these procedures take place. If the person does not consent in real time, his or her earlier consent is not valid. It is ethically significant that a person is conscious and consenting to a medical intervention when it takes place; in medicine, consent is not tantamount to the absence of objection. May the concepts of "implicit consent" and "presumed consent"

help? Implicit consent is relevant when a patient gives consent to a large set of interventions (e.g. hospitalization). Then, consent to minor aspects of the intervention is implicit; yet explicit consent to morally salient procedures is required. But, as said, it is unclear whether consent to hospital birth entails implicit consent to NBS. Presumed consent is invoked when direct informed consent is not possible, as in the case of organ donation. There is no reason to justify reliance on presumed consent when informed consent is possible. Rather, the contemporary doctrine of informed consent has matured in relation to ordinary and non-controversial medical interventions. Even life-saving surgery such as appendectomy for acute appendicitis requires informed consent, omission of which is considered negligent and disrespectful of personal autonomy and human dignity. This is so, even if the patient had expressed consent to appendectomy a few weeks earlier, in response to a hypothetical question about the possibility of acute appendicitis. Even women who choose hospital birth are not made to sign an advanced informed consent to cesarean surgery, should their doctors deem it necessary during labor.

Whereas some doctors may rely on earlier clinical encounters in which a procedure has been under proper discussion, that caring team in the maternity ward does not know whether the women's gynecologist actually informed her about NBS. As a matter of fact, there is paucity of research on the Israeli clinical encounter, let alone in the gynecological context. Whether the average gynecologist is aware of the new duty delegated to him or her by the 2009 Ordinance, and what his or her actual comportment, is unknown. This question is especially troubling because NBS is not part of the specialty curriculum in obstetrics and gynecology; nor is the rare metabolic conditions covered by NBS. An expert gynecologist is not authorized to offer genetic counseling either.

An additional concern regarding the division of information on NBS between the gynecologists, who provide pre-natal care, and the hospital obstetric department pertains to women who do not have routine pre-natal care. These may include two kinds of population – the underprivileged whose need for education and information is much more pressing; and those, on the other hand of the spectrum, that conscientiously prefer to avoid the medicalization of their lives. This latter group deserves to be informed about NBS upon hospitalization, especially when they give birth in a hospital due to medical problems (e.g. malpresentation), and not as a matter of choice.

Written information for pregnant women

A second level of information is the one written and distributed in pamphlets targeting pregnant women and/or fresh mothers. One such pamphlet bears a special legal standing since the Ordinance requires that every gynecologist provide it to the pregnant patient.

The brochure's title is "Towards birth", subtitled "including screening tests to healthy neonates". The topics discussed in the brochure are:

1. pain control during childbirth
2. episiotomy
3. medical examination
4. breastfeeding
5. smoking in the company of the baby
6. medical examination of the baby
7. administration of vitamin K, and antibiotics eye drops
8. vaccination against hepatitis B

9. NBS
10. Birth related financial benefits from the National Security Agency (the Israeli INPS)
11. Guidance program on baby care
12. Use of safety seats in the car
13. The *Drop of Milk* clinic

This list encompasses all key health related issues surrounding childbirth, uniting together maternal and neonatal needs. One such issue receives significantly greater attention than the others – NBS. This disproportionality is hinted at in the subtitle of the brochure. Altogether, NBS section is as long as all other sections combined. It is the only section that contains a URL (web address) in which more information is to be found. Even though mothers may refuse vitamin K, eye drops and vaccination, subsections titled “Is it possible not to perform the test”, do not appear in relation to vaccination and vitamin K. But such a subsection appears in the presentation of NBS.

The explicit emphasis on NBS and the timing of the brochure’s publication (May 2008), which coincided with the launching of the expanded NBS program, indicate that patient education on NBS was the real context of this publication. However, it was not written by the NBS program, but by the Department of Health Promotion in the Ministry of Health. It is unclear to what extent the need to educate expectant mothers on NBS was taken as an opportunity to communicate important issues, such as breastfeeding and safety seats, or, perhaps, couching NBS in the context of mainstream and well known issues, was a means to recruit legitimacy to NBS.

The brochure also sheds light on the construction of consent and refusal in the eyes of the Ministry of Health. Unless it is clearly life-saving, medical treatment of children is not mandatory and parents have the power to decline vaccination, vitamin K, eye drops and similar procedures. But this is a negative liberty, not explicitly recognized by the law. Hence, even though many mothers and activists call vaccination and vitamin K administration into question, the Ministry of Health does not see a duty to inform mothers about their power to decline these services. It is not evident that the moral and legal sensitivities regarding the expansion of NBS, persuaded the regulators to insert a formal opt-out option, thus altering the framing of consent to NBS from “full” negative liberty (i.e. the person may refuse but the establishment does nothing to either inform or help him or her) to formal opting out (i.e. the establishment makes sure that the person knows about the service and knows about his or her power to refuse it).

But formal opting-out may be conceived as “nudging” persons towards consent (see Cohen 2013). This is what the brochure does, by placing NBS within broadly accepted practices, informing the patient about her right to refuse, but not about the reasons that might support such refusal, the controversy regarding the expanded screening, for example. Because nobody thinks today that refusal to use safety seats is reasonable, contextualizing the information on the power to refuse NBS, actually represents such a choice as deviant and unreasonable, even if legal. This contextualization does not encourage mothers to explore the issue and to weigh dissent to NBS as a serious option.

The Israeli Ministry of Health chose the manner of framing. In the opening of the section on NBS, the brochure narrates,

Most babies are born healthy, but must undergo some medical exams, because few babies that appear healthy actually suffer from a treatable condition. Early

detection of the disease may prevent grave complications and severe mental retardation.

Indeed, this description fits well the pre-expanded program that aimed at the early diagnosis of PKU and hypothyroidism. Later on, after the sections on PKU, hypothyroidism and CAH (which is relatively common in Israel), the brochure writes under the title “Additional metabolic diseases”,

There are many inheritable diseases that are caused by inborn defects and that are not accompanied by [clinical] signs during the first days of life. Early detection and appropriate treatment may improve the developmental condition of the neonate. On the basis of international and local knowledge, an advisory committee determines which such conditions to screen.

We do not anymore hear about treatment, the prevention of severe mental retardation and death. The controversies about some of the new conditions included are not mentioned either. Following a two line section on the retention of samples for the purpose of quality control, comes the section on refusal. It tells the reader that,

If the parents refuse the proposed [screening] test, they have to approach a neonatologist during the hospitalization and sign a designated form after receiving explanation on the implications of not testing.

No choice is given to accept either the narrow panel (PKU and hypothyroidism) or a partially expanded one (e.g. PKU, hypothyroidism and CAH) only. The opting-out option is an opening for defection (or “exit”) from participation in the whole service, not about making a choice within the healthcare service.

The outcome of this policy is that a doctor-patient conversation about NBS by a physician who treats the relevant conditions is the privilege of mothers who make “different choices” – not to screen or to leave the hospital before 48 hours have passed from birth.

According to the Law on the Benefits of Birth (within the National Security Act, 1953), the National Insurance Agency pay the hospital for the hospitalization of the birthing mother “to the extent that the birth and its consequences render it necessary” (Table b1 in the Law). In actuality, following uncomplicated births, the mothers are discharged after 48-72 hours. This time framework is clearly linked to NBS. All mothers who wish to leave hospital before 48 hours have passed are made to sign a special form of self-discharge and to sign the NBS refusal form, with the instructions to come back for NBS or bring the baby to the local Drop of Milk clinic. It is noteworthy that even when no health problems exist, a mother who wishes to leave hospital after 36 hours, for example, is formally treated exactly like a patient who leaves hospitalization against her doctors’ best advice. As a matter of fact, NBS is the only medical procedure that warrants 48-72 hours of hospital stay. It follows, that the state pays a significant amount of money (170,000 births a year multiplied by 1 or more days of hospitalization) merely to secure the universal penetration of NBS, not even trying to send mothers home a little early and invest some efforts in making them bring their babies to an outpatient clinic for screening.

In the 1950s, the Israeli financial benefits of birth were attached to hospitalization. The National Insurance Security Law (1953) guarantees the payment of birth expenses related to hospitalization only, even if birth took place in a hospital out of the country. This was done in an effort to encourage poor mothers, especially Arab minorities and immigrant Jews, to shift from

home birth, which was typically carried out in dingy and dire conditions, to hospital birth.¹² This financial incentive was hugely successful – from a rate of 6% hospital-birth among minority women in the 1950s to over 60% in the 1960s (Shvarts et al. 2003). It is almost impossible to conceive these huge indirect costs of NBS, without the broader context of public health efforts to shift childbirth from the home to the hospital and to provide birthing mothers with a broad and strong protective social envelope.

Even though NBS is a procedure aimed at neonates, it is not intrinsically related to childbirth and maternity care. Rather, it must not be performed in conjunction of childbirth but at least two days afterwards. However, already in its very beginning owing to practical reasons, it was tied to maternity care. In Israel, which had already had a very powerful and paternalistic structure of maternal care, it was natural to add NBS to the uniform standards of childbirth, whose chief goal was the reduction in infant mortality.

For this historical reason and for the peculiarities of the Israeli regulation of home-birth, the governance and practice of NBS in the context of *contemporary* planned home birth is of very special interest. In fact, we have seen that the Israeli regulator gives special attention to planned home birth and to the execution of NBS in this context as well. Whereas the assimilation of NBS in the routines of hospital care has constructed NBS as a universal public health service, the mere choice of home birth is perceived as a threat to each and every link in the iron chain known today as “safe birth” by means of medicalization and institutionalization.

Before turning our attention to home-birth and the role of NBS in the social construction of birth, we wish to close the circle of information by the exploration of the post-screening

¹² This consideration is discussed in the minutes of the parliamentary committee on labor and welfare issues, July 20th, 2000. <http://www.leida.co.il/page.asp?id=20014> .

process of contacting mothers whose recently born children have been tested positive by the NBS lab.

Calling parents for retesting

When NBS gives a positive result, the National Center of NBS, where also the laboratory is located, is responsible to reach the parents of the baby. The lab's computer synchronizes with the national census registry in the Ministry of the Interior Affairs and with the hospitals' computer systems. This facilitates maximal coverage of data on new births. This flow of information is automatically checked against the flow of Guthrie cards (or forms of refusal). In 2011, there were 170,982 registered births, of whom 170,225 were screened. Of those who went unscreened, 127 were cases of refusal (0.07%), 43 were "undetected", lost to the NBS system (0.025%) and 587 who died prior to being screened (a perinatal mortality of 0.3%).¹³

The personnel of the screening lab tries to find out "missed children" and those whose screening results are positive. In the first case, they contact the local health services in order to locate the mother. In the case of first positive results of the test, they try to reach the family directly through the contact information provided, at the same time alerting the local physician authorized by the screening program.

According to information given orally by the chief of the newborn screening lab and service, Dr. Shlomo Almashano, all 43 "missing babies" belong to Jewish families who adhere to extreme anti-establishment life-style. They are all born out of hospital (in-hospital refusals are accompanied by the opting-out forms). Some are literally "lost" in the sense that officials fail to reach them; others refuse screening or refuse contact with officials before they know the issue at hand. One nurse who illegally practices home-birth sends the center Guthrie cards soaked with

¹³ http://www.health.gov.il/PublicationsFiles/newborn_2012.pdf [Hebrew]

blood obtained during circumcision. Because the MS/MS machine is not calibrated to this age group (eighth day post nately), the chief does not process these cards. However, one may wonder whether efforts should be made to accommodate these very few families who would not cut the child outside of the circumcision ceremony. Dr. Almashano knows of one child from this group of unscreened babies, who suffers from a disease that could have been detected by NBS.

Every positive screening result is communicated to the parents by either Dr. Almashano or by his assistant, who is a nurse with a master degree and licensure in genetic counseling. They have developed the strategy of communication.

In the following part we transcribe one phone call exchange between the director of the Center and a mother, whose child was suspected to have PKU.¹⁴ This conversation took place just before one of the interviews we had with the director, so that he reported it in the form of a direct discourse - what they said to each other -, repeating the sentences of the mother, as he freshly remembered them.

When the telephone call took place, the mother in question was not at home with the baby, but busy with errands in preparation for the circumcision. The baby was a male son and in the Jewish tradition, every son undergoes circumcision on his eighth day after birth. This is a very important and meaningful ceremony, where also the name of the baby is announced, symbolically integrating the newborn into the community.

The context is important, because it allows us to weight the "urgency" of the situation.

¹⁴ We were not informed about the identity of the family. This specific conversation was reported. We also had the occasion to listen to a few such calls, but only on the side of the lab.

The first request of the director is that the person be in a quiet area, where they can talk. In this case, he asks her to go out of the shopping center. Then he introduced himself as a person working for the Ministry of Health. He starts by recalling some data, like:

Director: I know that you had a baby on [date] at [name of the hospital]... Mazal tov [congratulations]... Do I disturb you?

Mother: I am doing the shopping for the circumcision.

Director: When will it take place?

Mother: Tomorrow.

Director: I would need you to come today to the medical center [name of a local clinics/hospitals] with your child.

Mother: Today? Why?

Director: Do you remember... when you gave birth, in the hospital, we took with a prick... a few blood spots of your child, to test him... it is something we do to every baby...

Mother: No, I don't remember, but possibly they did it.

Director: Well, I call you from the lab where we do the test. We look for normal growth and development of the child. When you feed the baby, his body breaks the nutrients into small parts in order to build up his muscles, his bones, his brain... We check that it works fine. Sometimes, if there is a problem, we try to help him out, giving him vitamins, for example, or prescribing a specific diet or we tell the parents to be more aware about specific food... In this case, we wish to see that the process works in your child.

Mother: That's it? Or there is more...

Director: Look, we are a lab. I am not a physician, I don't see children. We check the results of the test and, when something is a little off mark, we wish to check it again. The results can range from nothing to mild or more important outcome.

In this case, she starts reporting him about some difficulties she has with the child, such as that it is difficult to wake him up, that he does not eat well, but that she nevertheless started already to take his weight...

The director writes down what she is reporting about the baby, by making already association with the suspected illness.

Mother: All this... can be related to what you are telling me?

Director: Yes, it can. Now, what we need is that a doctor see the baby.

Mother: Does it mean that I have to go to the hospital with the baby? Does it mean that he will be hospitalized?... Should I go with the bag?

Director: In this case, yes.

Mother: Give me the name of the suspected disease, so I can look it up in the internet.

Director: As I told you, I am only reporting test results. Let me worry about it. This is my job. You do your part, make the child see a doctor.

This woman lived in Kfar Saba, a city located between two tertiary care hospitals, Rambam and Shiba. The director asks her where she prefers to go. Once she answers, he tells her already the details of the appointment for that day, the hour in which to show up at the emergency department and the name of the physician that will be waiting for her and the baby at the door.

Director: From my experience, you may have some understanding or questions now, and more or different questions later. So, I give you my cell phone, in case you want to call me.

Mother: Can you repeat your name?

Director: Of course. Dr. Shlomo Almashano, from the National Screening Center. My cell phone is [telephone n.]. You can call me anytime for any question. If it is related to symptoms of the child, better to call the doctor. Otherwise, you can call me whenever you want.

Mother: Even at 5 in the morning?

Director: Yes, even at 5 in the morning.

From this reported conversation, and some of the comments to it made by the director of the Center, we learn a few important elements of the communication process that takes place in this occasion.

First of all, the person calling from the Center always verifies the identity on the other side of the telephone. In fact, if it is a fix number, many people can answer first. They do not tell anybody else that they are calling from the Center, unless it is one of the parents. In case a third person answers, they ask to talk directly to one of the parents, usually the mother. The preference given to the mother is related to the higher probability that the child be with her more time than with the father.

The director of the Center explains that his strategy of communication has two main purposes. The first one is to prevent over-reaction and to convey reassurance in addition to the evidently worrying news. But in parallel, he urges her to go to the hospital with the baby. This second goal is pursued differently, depending on the case at hand and its estimated emergency.

The first purpose is achieved by telling her that it is a test, to which every baby is subjected; that questionable results of this test are routine and most retesting proves negative. His

key message is that if indeed the test is positive, the condition is treatable, perhaps preventable. Put in other words, the first message normalizes the event, communicating the routine nature of such calls after the birth of “normal babies”. The mother’s experience is not unusual. (As a matter of fact 2% of babies are called for retesting). The second message addresses directly the ominous content of the call while simultaneously recruiting compliance. This is not a call communicating “bad news”, but the good news of available effective care in case the baby does have a problem. The bottom-line directive message is to bring the baby for retesting as soon as possible. The director also tells the mother that the clinic or ED doctor have been informed and will wait for her personally.

Not all mothers are sent for retesting with the same degree of urgency. The NBS center classifies positive test results into 3 different categories. This classification comes from the combination of two criteria – the numerical value of the test (or the distance of the values from the "normal cut off", which usually reflects the statistical likelihood of true positive) and the nature of the suspected condition. The most urgent category is comprised of a clear positive result of a potentially devastating disease, such as PKU. In such cases, the center immediately alerts the local doctor responsible for NBS and arranges that he or she meet the mother in the emergency department. As explained in chapter four, every hospital cooperating with the NBS program must have a 24/7 expert physician on-call for this very purpose. Interestingly, when other diseases of infancy are suspected, the Israeli healthcare system does not provide for a dedicate on-call expert. For instance, if a one year old baby is suspected of having diabetes mellitus, the family will be sent to the pediatric ED, with the expectation that the system detect the urgency of the condition and process the case without any particular expert dedicated to the suspicion.

An indirect message of urgency is borne out by the insistence not to wait until after circumcision takes place, for instance. Because the date of birth is unpredictable, and circumcision takes place on the eighth day of life, the family has very little time for arranging the party. Signs of weakness or illness are a reason for the postponement of circumcision. Hence, timely circumcision is a cultural sign of good health and an auspicious start in life. In addition to the discomfort caused to the busy family and the doubt inserted into the preparations for circumcision, sending the baby for medical tests in the hospital casts a grave shadow over the cultural construction of the baby's health (Klein 1998, 182-184). Precisely because of the interruptive nature of the request for immediate retesting, the mother grasps well that the insistence on immediate testing is really imperative. Nobody in the healthcare system would disturb the preparation for circumcision unless something really urgent was at stake.

A third level of emergency is considered a mild alteration – a borderline result that falls near to the cut off line and which might be explained out (for example, because of the low weight of the baby at birth). Important clinical information, such as the gestational week and the weight at birth, is known by the Center and it is factored in during the first reading of the results. As a matter of policy, the center considers every abnormal test as urgent until the baby is brought to full diagnosis. With the accumulating data on the neonates, tests values and ultimate diagnosis, it is possible to modify lab-cut offs and even create dynamic ones (e.g. different cut offs for different birth weights) so as to reduce the rate of false positive results. Following such a strategy, for instance, the normal line of TSH was altered, with the consequent reduction of 50% in false positive results and without missing a single sick child. This is a huge difference, because the original rate of TSH retesting was 0.75% (1275 babies annually). Six hundreds babies were spared retesting in 2011.

Tests results that fall in between the first and third category are relegated to the mid-level degree of urgency. A typical example is CAH.

One more "internal rule" about the content of the communication is that the suspected condition not be revealed to the parents at the stage of initial communication. This is done with the intention of preventing excessive worry and self-searches of the internet that may expose parents to "catastrophic scenarios". The NBS center person calling the parents, kindly, but firmly, sets limits on the communication, describing their role as readers of lab results, thus avoiding any advice other than referral to a relevant expert physician. According to the chair of the lab and his assistant, some people follow their instructions without further questions, but in most cases, people inquire more than once. They call the Center with questions, usually before going to the hospital or clinic for the appointment. In fact, after the first conversation, for example with the mother, the father would call in order to "understand better" what is going on. Not to mention the cases in which, relatives and relatives who happen to be healthcare workers call and press for more information. Even in these cases, the suspected disease is not revealed, but the parents are requested to go to the appointment.

On one hand, the center reiterates its round the clock availability for further questions; on the other hand, it never reveals the particular suspicion.

All the relevant medical information collected during the telephone conversation, such as the description of the state of the baby, is reported by the Center to the physician waiting for them at the emergency door. The Center is also informed about the effective coming of the mother/baby at the hospital. The small circle of professionals involved in metabolic diseases of childhood and in NBS renders their relationship personal, even intimate. Every case detected by

NBS is a source of professional interest and is accompanied by formal and informal communications between the NBS Center and the local personnel.

In sum, the overall patient communication is a delicate balance between informing without telling all the data in hand; it is a balance between directedness and reassurance, where urging the mother to go to the hospital is accompanied by the hope that nothing important is happening. It is not easy to maintain such balance, because, whereas the policy of communication is quite uniform, perhaps even rigid, the parents involved come from very diverse personal and cultural backgrounds.

Home birth

A different scenario whatsoever is the case in which delivery takes place at home. This is highly relevant to NBS, because as long as NBS is construed and performed as a hospital based program, then its shape and modality of administration might be altered once it is taken out of this context.

The home birth under discussion are carried out by women who benefit from easy access to modern hospital birth, but conscientiously choose to deliver the baby at home, relying on hospital backup only in case medical needs arise.

During the first six decades of the twentieth century childbirth in the affluent world moved from home (95% in 1900) to hospital (>97% in the late 1960s) (DeVries 1996, 35). A reversed trend began with the counter-culture and hippie movements of the late 1960s and 1970s, when feminist and anti-establishment movements criticized the “medical approach” and the consequent medicalization of childbirth. In some developed countries, such as the UK and the Netherlands, home birth have always been a mainstream choice and available service, even when

chosen by a minority of women. In Israel, home birth started to regain currency in the 1990s, led by midwives who were either exposed to the alternative American trends or came from the English tradition of holistic primary care, of which home birth attended by general practitioners and lay midwives is normative.

Until the middle of the twentieth century, most births in Israel took place at home. Zionism and its socialist version introduced the practice of birth-clinics or birth-centers, where women gave birth under some medical attention and stay there to recover for some days, sometimes weeks. With the development of modern biomedicine, these centers were eliminated and incorporated in hospitals, because it became too expensive and impractical to supply these centers with CT scans, neonatal intensive care and other technological aids that have become integral to “modern” or medicalized birthing.

The most significant change in birth care in Israel took place in the 1950s when the government supported a hospital birth policy with the intention of reducing the relatively high mortality among two large population groups – Israeli Arabs and nearly a million Jewish immigrants to the young state of Israel, mainly from Middle Eastern countries, who lived in temporary and dingy transitional camps (*ma'a'ba'rot*), waiting for the construction of modern housing (Shvarts et al. 2003). This transition led to the virtual disappearance of the “wise-women” / traditional midwives who governed childbirth in the traditional Jewish communities in the diaspora (Barilan 2014, ch. 6-7).

In the late 1990s a few certified and well-experienced Israeli midwives began offering home-birth care to women who conscientiously chose not to give birth in the hospital. The 1929 Midwifery Ordinance, issued by the British authorities of Palestine was quite permissive. In order to practice as a midwife, one needed to have completed at least six months of study in a

recognized midwifery school. Until the 2000s, there was no legal distinction between home and hospital midwifery. The ordinance prohibited midwives from attending “extraordinary cases and birthing women who are sick” (clause 12). It actually anticipates the home-birth movement in its distinction between “healthy and natural birth” from pathological cases. Only the latter required medical attention.

However, it has been very difficult to revive homebirth in Israel, practically because the Israeli National Insurance law (1952) and other governmental structures paid mothers their birth bonus support¹⁵ and reimbursed care only for hospital births. Those giving birth at home receive neither direct support nor reimbursement of any medical expense, however minor relative to the costs of hospitalization. Every birthing woman qualifies for two nights hospital stay, even without any medical need on behalf of either mother or child. These arrangements constituted a major incentive pushing women away from home birth. Apparently, growing awareness of “natural birth” and mounting dissatisfaction with biomedical birth have pushed some midwives and birthing women to pursue home-birth as a fully private service. In the 2010s, over eight hundred babies, 1% of all deliveries, come to the world within the context of planned home birth attended by a certified midwife.

Even though temporary shelter camps and related socio-economic problems have disappeared from Israel in the 1960s, the Ministry of Health has remained explicitly hostile to home birth. The first ordinance regulating homebirth in Israel appeared in 2008 and was updated in 2012 (appendix number 2). Its preamble states that the Ministry of Health considers hospital births safer than home birth. However, “...in light of the fact that home deliveries are performed

¹⁵ This is a one-time sum payable directly to the mother in the range of a few hundred Euros. Its nominal value has changed many times. The official name is מענק לידה – *ma'a'nak lei'da*.

in Israel...the ordinance aims at balancing the woman's freedom to choose and the safety of both mother and child (who does not benefit from the freedom to choose).”

For a few reasons, we have found home birth significantly relevant to the understanding of NBS, especially in Israel. First, the regulations in force (the 2008 and 2012 Ordinances) were issued in parallel to the introduction of expanded NBS in Israel. Second, even though screening takes place at least two days after birth, in a time-window never attended at all by midwives, and even though NBS is not related at all to midwifery, and even if the ordinance requires a home visit by a pediatrician within 24 hours from birth, the ordinances place the responsibility of NBS in Israel wholly on the shoulders of the home-birth midwives. They must inform the women, process the screening, send it to the central NBS Center or make the woman sign the dedicated informed refusal and mail it to the NBS center, should she opt out of screening. The reasons for this are most probably pragmatic.

The Israeli National Security Insurance (*Bi'tu'ah Le'u'mi*) pays the hospital a flat rate of 9000NIS (close to 2000Euro in 2013 exchange rates) for every simple, uncomplicated birth. As a policy, Israeli hospitals discharge the birthing women 40 to 48 hours postpartum, after NSB has been performed. This duration of hospitalization obviates screening because it does not require special visits in a clinic and because it allows the performance of the screening by experienced professionals. Mothers who insist on early discharge are made to sign a special informed consent to leave the hospital against physicians' advice and also to sign the special form dedicated to refusal of NBS (appendix 4). They are instructed to perform the NBS once it becomes technically possible. Undoubtedly, this procedure has significant psychological effect on the women, actually misleading them to perceive early discharge as potentially dangerous, and in par with non-compliance with good medical care.

At this stage we may observe that NBS have become the closing event of the biomedical Israeli birth – a process beginning in a hospital, terminating after two days (more or less) with the screening of the child. We may also observe how the regulator has transferred this structure to the very different context of home birth. From the perspective of Israeli law, birth – be at hospital or home based – terminates two days after delivery, with the concluding act of screening.

It is an ironic twist that the Ordinance governing home birth, declares that *with regard to newborn screening*, the midwives bear the responsibility of a hospital director. Because the Ordinances governing NBS nominate the hospital director as the ultimate responsible for NBS, outside the hospital, this role is relegated the midwife. We find the pioneers of de-medicalization of birth, and those who struggle to move it back to the home-setting, receiving legal recognition only at the price of accepting a role of a “hospital manager”. The universal mission of NBS and its regulation by the Ministry of Health have constructed NBS as a both birth-related and hospital-based practice, as if no other alternative for its implementation exists.

In addition to the practical and legal aspects of the conceptualization of NBS in Israel, we have had a hypothesis regarding home-birth and NBS. Since refusal of NBS is very rare (less than 1%), it is very difficult to tackle it methodologically. Researchers must tend to thousands of births in order to come up with a significant number of refusers. Even then, it is quite likely that mothers who opt out of NBS, may not wish to cooperate with biomedical academic research.

However, we have also hypothesized that since women who choose to give birth at home are likely to be mindful of their power to choose and inclined against “mainstream” biomedical management of birth (or even health), a relatively large concentration of NBS dissenters would be found among the 800 women or so who give birth at home. We have also hypothesized that

NBS is a good test-case of the construction of “birth” and its boundaries in the worldview of home birth women and midwives.

After months of efforts at securing the confidence of *I'ma'hi*, the association of homebirth midwives in Israel, we have embarked on a series of in-depth interviews of the fourteen licensed and active home-birth midwives in Israel. Saturation has been achieved with the seventh interview. In this section we report our findings regarding NBS.

Our primary finding was that, against the hypothesis linking home birth with dissenting and personalized choice in health-care in general, certified home-birth midwives and “their women” (as they call the people they serve, explicitly avoiding the term “patient”) are quite compliant with NBS. In fact, the opposition to “medicalized birth” is supported by the belief that birth is a non-pathological event in the life circle. But this opposition to medicalization does not apply to NBS since its construction falls outside the scheme of “normal life”.

Few midwives explicitly express this distinction between normal/pathological, natural/medical. For example: “This [NBS] is about sick children” (midwife no. 4) and “This is a matter for professional doctors” (midwife no. 7). Normal processes need to be “accompanied”, but pathological ones must be addressed medically.

Home birth midwives are opposed to the medicalization of “natural” birth, not to the medicalization of anything construed by society as “pathological” or abnormal, thus differentiating “medical” interventions aimed at “pathologies” from lay care (i.e. homebirth midwifery) that is about “normal” and “healthy process”.

The word “normal” is key to the midwives’ narratives and appears numerous times all over. Sometimes, it indicates the absence of pathology. At other times, it simply refers to rare and unusual occurrences. Midwife no. two explains with regard to NBS:

I don't recommend because, you know what, I'll tell you why. I don't feel that I understand it enough. I'm not a doctor for such diseases. I never in my life encountered it you know. I know that the doctors, when they hear about it, they get very excited. They don't like at all the idea that the baby is not protected or something like this.

It may be observed that in a professional identity that is chiefly based on personal experience, it is impossible to actively endorse an intervention that is aimed beyond one's own personal experience. In this sense the extreme rarity of the screened for disease already renders them an "abnormal" issue. In the second sense, because NBS targets "diseases", it belongs to the doctors' realm, not to the territory of midwives tending to and ordinary and healthy life-event.

Interestingly, NBS is not classified according to its actual target of intervention (i.e. all neonates, the vast majority of whom are healthy) but according to its ultimate goal and context of practice (i.e. sick children and the science of rare metabolic diseases).

An even more interesting finding is that "empowerment" is context-dependent. While the context of "home-birth" is the power of women to choose regarding their own process of birthing, home-birth midwives seem not to be open to personal choices in *other* healthcare contexts, even if somehow related to birth. For example, midwife no. 5:

I once, maybe every five years. Have a couple that says we are not going to do this [=screening]. They are not going to circumcise the kid,¹⁶ and they are certainly not going to give blood to anybody.

¹⁶ Over 90% of Israeli parents circumcise their male babies. Circumcision is the most widely observed religious practice, even among many secular and atheist people.

In such a case, the midwife said, she offers detailed explanation about the risk of metabolic diseases, with the intention of helping them make an informed choice. However, midwife 5 explained why in actuality she hardly has refusals,

We have incredible power as midwives...they have known us [throughout] the pregnancy...they trust us. We have an incredible ability to give them information and to help them make an informed choice.

Midwife no. 3 reported the largest number of refusals in her practice, five in over twenty years of experience. She made them all sign the dedicated dissent form. She explains that they were all “very very religious”, with a spirituality that considers medical tests and interventions as lack in wholesome trust in God.

Other midwives were more explicit in their lack of tolerance of deviance from *their* standards of safety. Home birth midwives advocate for personal choice about the place and kind of birth, and quite happy with diversity of a certain kind of birth related choices (e.g. position, presence of lay attendants etc.); but they are quite directive, even restrictive, with regard to deviance from their own standards of safety and good practice. Why don't these midwives sympathize with refusal to NBS? We may point out three explanations.

According to the first explanation, whereas the biomedical establishment has associated NBS with birth, home birth practitioners do not see it this way. Hence, intensified efforts at the demedicalization of birth has left aside the problem of neonatal care and its proper medicalization/demedicalization balance.

Second, even regarding birth, all of the seven midwives interviewed refuse to participate in a childbirth that is planned against their “red lines” of safety. These red lines vary from one midwife to another. Some personal choices make borderline cases. For example, very rarely, a

woman wishes to give birth all on her own, with a midwife on-call in an adjacent room. Only one of the midwives interviewed would accept such a choice and only if the alternative is unattended birth. Even though the risk of non-screening is relatively low, it is still unacceptable by people who are committed to show that home-birth is a safe-choice and do not want it be associated with an adverse health outcome of any kind. In relation to NBS, all midwives support the practice; and all of them tolerate refusal to screen. Their professed personal policies uniformly mirrors the Ministry of Health's.

A third, complementary, factor is the midwives' respect for women's choice about their own bodies and health, even when such choices may implicate the baby in utero, and the midwives' independent sense of responsibility for an already born child. As most midwives explain, the born child is "independent" of the mother. Nevertheless they accept parental authority,

If they refuse, they refuse. It's their baby; their choice. (Midwife no. 1).

These factors overlap and interact with each other. All of the interviewed midwives addressed NBS in terms of advanced technology, progress and professional authority. Even the one midwives admitting to have "mixed feelings" about screening (not differentiating pre-natal from NBS), says she recommends NBS:

I am trying my best to convince them [=to comply with vitamin K prophylaxis and NBS]...basically, we are not third world. (Midwife, no. 1)

All midwives were aware of a baby, delivered at home, who had been diagnosed clinically after his parents refused NBS. But the case was not cared for by a certified home birth midwife; and they did not know the details.

One last factor to influence their pro-active attitude towards NBS is the image of complete preventability of the pathologies covered by NBS. In relation to childbirth complications, they stress the probity of trusting “natural birth” with acceptance of the inevitable occasional misfortune. But the halo of complete preventability bears a special allure with it which the midwives cannot and would not resist – the prospects of catastrophes that medicine may prevent in advance. Put in other words, since complications occur in hospital births as well, the midwives do not find its promise of safety a genuine advantage. But since NBS wears a face of complete and risk-free success in the prevention of catastrophes, there is no reason to think of alternatives. Indeed, all midwives refer to NBS by synecdoche, as “the PKU [test / procedure]”. When the NBS Center’s personnel call up families, they also use this expression by introducing themselves as the “PKU people” (interviews with the head of the center and his assistant). This tag obliterates the distinction between NBS and “expanded NBS” and represents the expanded panel (along with its pilot arm) as “life-saving” as timely detection of PKU, thus invoking the most compelling duty of all – immediate rescue of a person in mortal danger.

In sum, from the interviews with home birth midwives we have found out that valuation of patient choice should be contextualized. Focus on one kind of empowerment (e.g. home-birth) may not be accompanied by increased empowerment in other, even related spheres of healthcare choices. Rather, the focused struggle to legitimize it, may actually constrain choice in other spheres of action. Home birth midwives construe NBS as an activity related to “pathologies” rather than a “normal, natural process”, connect it to a body of knowledge that stretches beyond their personal experience, and associate it with technological progress and the utopian promise of “complete” prevention. Most importantly, the midwives do not connect NBS to childbirth but consider it an independent aspect of neonatal care, and usually a life-saving at that.

CHAPTER SIX: NBS BETWEEN PUBLIC HEALTH AND CLINICAL PRACTICE – A MODEL FOR PUBLIC PARTICIPATION IN PROGRAMMING

This chapter was written in collaboration with Dr. Anat Gofen, Lecturer in Political Science in the Hebrew University in Jerusalem.

Introduction

In the last few decades every baby born in the developed countries (and in many developing countries as well) has been subjected to a panel of blood tests aimed at the early detection of some inborn diseases. The procedure is known as “newborn screening” (NBS). In the 1970s and 1980s, newborn screening was considered an uncontroversially successful public health initiative. In the past twenty years screening has been expanding at three different levels: more conditioned are screened, larger populations covered (as more countries initiate screening) and additional biochemical and genomic technologies employed. Public debate and regulative structures of NBS have been expanding as well, reflecting growing awareness of the ethical, legal and medical aspects involved.

As a matter of fact, two processes have been developing in parallel to each other – the maturation of the doctrine of informed consent and the advent and expansion of NBS. The maturation of informed consent is part of a broader turn towards human-rights based medical law, and the expansion of NBS is part of the revolutionary interaction between biotechnology and information technologies. No less important are the roles of two social phenomena that loom large over the construction of NBS services – the emergence of patients’ advocacy groups, and the transition from home-birth to hospital birth. The temporal coincidence of these and other factors have molded the NBS systems and its ethos of practice.

The first NBS service developed as a local initiative in Massachusetts. The layout of this first program (e.g. the decision to screen universally, and not only babies at risk), and the 1968 WHO “Wilson and Jungner’s criteria for medical screening”, combined into a master framework for all future NBS programs. But because the expanded programs posed a challenge to the established framework and guidelines, intensive efforts at public participation in the reframing of these programs took place, mainly in the format of advisory committees.

These efforts resulted in a sort of contradiction. On one hand, almost each state and jurisdiction has employed different structures of public participation in the regulation of NBS (Jennings and Bonnicksen 2009); on the other hand, academic scholars, activists and regulators have expressed dissatisfaction with the guidelines that sprang forth from diverse modes of participation. They actually protest against the absence of uniform standards for NBS, and behold such standards a desired near-future goal (Padilla and Therrell 2012; Loeber et al. 2012; Burgard et al. 2012).

As we have seen in the chapters on the Israeli program, direct public participation was virtually non-existent. However, the professional committee that was created and nominated on the occasion of the expansion dedicated significant amounts of efforts to study NBS programs and labs worldwide and strove to learn from their experience overall. Interestingly, the Israeli program contains some unique normative features one would expect coming from an ethics committee or similar form of public involvement. Central to these features are the emphasis made on the duty to inform and on instrument of information as well as the information about the power to opt out from the service. But precisely these novel and ethically oriented regulative features highlight deeper or more comprehensive ethical questions. For example, why is the only choosing power given to consumers (i.e. neonate’s parents) is non-participation?

In this chapter we wish to offer an outline for public participation in NBS in a manner that is open to pluralistic modes of governance within a relatively coherent and unified set of basic values. This task will draw insights from the lessons taken throughout this thesis and with additional aid coming from science and technology studies, the “discursive dilemma” (List 2006), the “citizen participation ladder” (Arnstein 1969) and the “personalization” of public services (Needham 2011).

Aiming at deliberative processes, we will focus on interrelated key issues that shed light on the current ethical problems – the remit of the service, and its “moral externalities”. From the perspective of public health, it is not necessary to make the extra efforts to reach universal coverage (e.g. the marginal utility of reaching out to babies born at home might be too low relative to the expected benefit); but from the remit of a public commitment to “save” and not leave behind a single vulnerable baby, no-matter how difficult it is to trace him or her, the ambitious paternalistic outreach at almost any cost does make sense. We refer to “moral externalities” as the unintended and unaccounted for moral (and other) price in one domain that results from a policy in another. The skimpily explored ramifications of NBS on the duration of hospitalization after birth are an example of such an externality.

Our working hypothesis is that exploration of these conundrums is prerequisite for effective public participation in the construction of democratic consent (i.e. legitimization) as well as personal consent (i.e. the particular instrument of consent¹⁷). Evidently, deliberation is

¹⁷ Full informed consent, “opting out”, presumptive consent of the neonate if he or she were able to make a choice, parental right to privacy in making health-related choices on behalf of their children are some examples of “instruments of consent”.

one kind of public participation; focusing on deliberative processes does not exhaust the democratic commitment to either participation or human rights.

Because the bioethics discourse has developed as a dynamic, its normative discourse may be regarded as a form of public participation as well. Overall, a better understanding of NBS policies may contribute to the broader question of programming health-related public services and their construction of patient consent.

We open this chapter by an exploration of the nature of NBS, arguing that although it is a public health care service, it cannot be classified as a public health service only. Indeed we will show how NBS has evolved as a hybrid of public health service and clinical care. In this light we will examine some models of public participation and offer one of our own, along with some theoretical considerations for the evaluation of their ethical effectiveness and deliberative approval.

Newborn screening between public health and clinical care

Because they are both preventive medical interventions administered universally and uniformly to individual people, it is tempting to compare NBS to immunization and to behold the ethics of NBS through the prism of balancing personal autonomy against power of the state as a promoter of the common good.¹⁸ However, reflection on the meaning and policies regarding non-compliance will shed light on the fundamental differences between the services. Non-compliance with immunization differs from non-compliance with NBS in at least three substantial ways.

¹⁸ NBS was born as a universal, mandatory and state-directed service in the same state whose compulsory vaccination law was upheld by the United States's Supreme Court in 1905 - See Gostin 2005 and Mariner, Annas and Glantz 2005.

First, non-immunization might pose risk to others; second, because non-immunized children benefit from the herd immunity of others, non-immunization involves a “free rider” set of problems; and third, whereas massive non-immunization brings forth a substantial risk, abolition of screening carries a very low risk (in the range of 0.1% per non-screened baby).¹⁹ It is also noteworthy that the success of immunization programs has led to the shrinkage of the panels recommended and to growing tolerance of parental choice, while the success of NBS has been associated with expansion of the program and intense efforts to reach each and every neonate.

The era of expanded NBS was ushered by healthcare professionals and patient advocacy alike, but it has been accompanied by loud critical voices coming mainly from the direction of bioethics and citizens’ rights movements. Four interacting factors are responsible for the transition of NBS from a celebrated life-saving service to a problematic social system. The first is technical. The more conditions screened, the more questions emerge; the more sophisticated is the system, the more questions arise regarding lab standards, incidental findings, storage and the like. The second ensues from the shift from a core practice that is focused on the most obviously beneficial and urgent to an expansive mind-set that strives to include every potentially relevant

¹⁹ In U.S. law, “imminent danger” may warrant state intervention in parental decision power over their child (Horwitz 1979-1980, 272). Unique to NBS is the question whether a test aimed at finding out whether the child is in “imminent danger” warrants the coercive power of the state, especially when the risk is quite low.

It is noteworthy, that the estimated risk of 0.1% pertains to hypothyroidism only. Risk for PKU is ten times lower, and the risk for most conditions screened by MS/MS technology is lower than one 1/100,000. It follows that abrogation of the MS/MS technology bears an extremely low risk per child.

condition. It is a conceptual transition from parsimonious service to exploration of its limits and boundaries. Most far reaching, perhaps, is the indirect impact of NBS on childbirth and its costly medicalization. Already in 1965, when the rate of hospital birth in America was at its peak, the American Academy of Pediatrics recommended that screening be carried out prior to the baby's discharge from the hospital (Committee on Fetus and Newborn 1965). Because screening for PKU (and some other conditions) cannot be carried out prior to forty-eight hours post-natally, and because insurers tend to set strict limits on hospital stays, NBS has rendered a 2-3 days of hospitalization a universal standard for uncomplicated birth. Undoubtedly, shorter hospital stays or home-birth do not exclude the possibility of NBS, but hospital birth is evidently the only way to ensure cheap and universal screening of every newborn (Braveman et al. 1995). Thus, NBS soaked its appeal as a public policy (rather than a fee for service offered by doctors on an individual basis) from the practice of universal hospital birth and shaped the standard range of hospitalization in a society that has enshrined hospital birth as the standard of birth (DeVries 1996). The key motto of both NBS and hospital birth is a unified standard that guarantees protection from rare complications; it is about a pathology-oriented cultural construction of childbirth, of gearing up the natural event of birth in preparation for the worst, so as to optimize overall safety, even at the price of minor complications and occasional discomfort. Routine physical exam by a pediatrician and hearing tests of every newborn are additional forms of screening. The standard of 2-3 days of hospitalization also fit the recommended period of "medical observation" prior to discharge (e.g. Britton, Britton and Beebe 1994). Thus, the waiting period mandated by NBS has become a screening instrument in its own right and a template for further screening tests to monitor for possible medical complications (e.g. Eggert et al. 2006). Even though all of these tests and procedures deserve the title "screening" (the

application of a test on an asymptomatic population with the intent of detection of a hidden medical problem), only the heel prick sampling of blood for biochemical disorders belongs to the system and rationale of “NBS”.

The third factor behind the emergent criticism of NBS is the maturation of bioethics and rights oriented approach to bio-law. Whereas in the 1960s a few scientists and activists were able to introduce a universal and mandatory medical service, the 2000s are marked by heightened awareness of public participation and informed consent. Some critics propound the transfer of NBS from the conceptual and regulative schemes of public health to those of clinical care (Ross 2011). However, the dichotomous division between public health and clinical care might not answer key ethical problems. Rather, the fourth factor behind the emergent controversies on NBS seems to be the chimeric nature of NBS as fitting and unfitting both public health and clinical care.

Typically, in clinical medicine, bodies of medical knowledge on diagnosis, prognosis and care are consolidating from the teachings of basic science, clinical research and cumulative experience. Although the interactions among science, medical services and culture are complex, personal choice of patients and lay people has marginal role in the canonization of medical textbooks, guidelines and similar standards of practice. Patients’ involvement takes place in the clinical encounter, which is the arena where caregivers present patients with recommendations culled from standardized knowledge, and try to tailor with each patient personal decisions of healthcare (e.g. selection of antihypertensive medication or choice between surgery and observant policy). Ideally, decisions are made in a process of “shared decision making”, usually in the form of informed consent to every significant intervention, and implicit consent to care overall. Not only do acts of care require consent, but the therapeutic relationship also depends on

a person's choice to be a patient of a particular clinician or healthcare service. Clinical research is an optional addition to standard care; but the latter is never conditioned on the former. Clinical research depends on special regulation (IRB) and specific informed consent.

From this schematic description, we may discern two stages of clinical decision making. In the first, bodies of "professional" knowledge are created independently of individual patients, whose active participation becomes crucial and detailed only later, in the actual care of each person. This individual participation constitutes the second stage of clinical decision making. The transition from standardized knowledge to a personal healthcare plan passes through the doctor patient relationship.

However, NBS does not fit this paradigm. First, in NBS, the patient neither suffers from any symptom nor seeks medical attention. Expanded NBS involves a large number of very rare conditions, of which the ordinary person has skimpy awareness at best. Even if a healthcare professional is keen on and capable of elaborate patient education, the parents' set of mind may not be receptive to serious contemplation of testing their newborn baby for a wide set of improbable and unfamiliar diseases. In order to cope with this difficulty, recent reports and policies recommend that patient education begin early, during pre-natal care, for example, and that the authorities use the media to disseminate "educational material" to render NBS common knowledge (AAP Newborn Screening Task Force 2000, 409). But as long as this does not happen, and we do not have evidence of appropriate patient awareness at the time of screening, we have good reasons to doubt the relevance and validity of "consent". It might be the case that parents are neither cheated nor coerced; and yet the notion of genuine informed consent to screening for dozens of metabolic diseases is implausible. Indeed, leading professional and

public bodies have doubted the practicality of informed consent to NBS (AAP Newborn Screening Task Force 2000, 409).

Lastly, because medical knowledge of many of the conditions screened is still evolving, there is no “standard of care” in relation to NBS. Therefore, some critics argue that in many cases it is impossible to conceptually separate expanded screening programs from clinical research (Ross and Waggoner 2012). Perhaps, only through universal screening of extremely rare conditions will it be possible to trace a minimal number of “affected” people so as to allow proper knowledge of the natural history and treatment options. Put in other words, we face a circularity in which the ultimate justification of NBS might depend on its universal penetration.

In sum, while in clinical care, a patient ideally gives an informed consent in a process of shared decision making to a scientifically sound procedure, in expanded NBS, people who have not chosen to become patients (or: render their babies patients), have little power regarding a procedure, which has a long tail of disputed benefit and evidence based validity.

Deep and shallow empowerment of public participation and individual choice

From its very beginning, the expansion process has been accompanied by significant deliberation and public participation (Hiller, Landenburger and Natowicz 1997). These may assume different shapes and consequently different outcomes. For example, Bernhard Wieser compared the regulation of NBS in the UK and Austria (Wieser 2010). In the UK, screening is regional, overseen by a dedicated National Screening Committee that communicates scientific information to the public. In Austria, the program is centralized, overseen by a medical board advising the government on a variety of biomedical and environmental issues, communicating to the public legal and political information. Drawing on Sheila Jasanoff’s theory of social epistemologies in

collective decision making in democracy, Wieser concludes that each society has a distinct approach to the relationship between information and legitimization. In the UK, the authorities' appeal to public reason hinges on open communication of scientific and technical knowledge; in Austria, the authorities claim legitimacy for their NBS program through the exposure of its legal, political and administrative foundations, structure and oversight.

However, it is not clear whether any relationship exists between the cultural and social modes of planning and legitimizing on the one hand, and the programs' ultimate structure on the other. Moreover, the transition from descriptive analysis of processes of legitimization to normative conclusions is still undecided. One may endorse each method of democratic public participation as equally legitimate; but an Austrian might wish to know whether the Britons have a better and more ethically sound program or vice versa. He might wish to know whether the notion of an overall "better" program is meaningful at all. In the USA, lack of uniformity of NBS programs across all states has been considered unethical and unjust.²⁰ Possibly, no other medical service is mandatory in some democratic jurisdictions and depends on full informed consent in others. The cohabitation of both extremes seems to outstretch ordinary diversity in public reason. How is it possible to know whether different outcomes of democratic deliberative processes are equally ethical, and whether the co-existence of different programs reflects pluralism or mismanagement?

Recently, an attempt towards unification has been taking place in Southeast Asia, Oceania and the EU as well, with much emphasis on the value of standardization of laboratory and clinical practice (Human Genetics Society of Australia 2011; Padilla and Therrell 2012;

²⁰ See US Department of Health and Human Service website

<http://mchb.hrsa.gov/programs/newbornscreening/screeningreport.html>

Loeber et al. 2012; Burgard et al. 2012). Whereas uniformity of lab standards is an obvious scientific and clinical goal, the ethical and legal aspects of the program seem to call for balancing pluralism with universal norms, such as fairness, protection from harm and respect for persons.

Perhaps, some jurisdictions care only for a “minimal liberal accountability” which is a majority based consensus on a problem in hand, not seeking underlying justification and harmonization with other, even related, regulative issues. Other jurisdictions seek a “comprehensive deliberative account”, which requires deliberation and agreement at the level of values, reasons and legal coherence. For example, so long as regulation is the product of democratic governance, the “liberal account” might tolerate absence of informed consent in NBS despite the centrality of informed consent in clinical care and medical research. But the “comprehensive deliberative account” would insist on coherence, demanding either the application of the same standards of informed consent or justifications for the difference. The co-existence of ethically inconsistent public choices constitutes the “discursive dilemma”. Societies that value pluralism and free individual choice might be more tolerant of such inconsistencies than societies that seek shared moral foundations (List 2006). However, we observe that the growing role of civil and human rights in bio-law and its growing presence in the criticism of NBS policies pushes policy making in the direction of the “comprehensive approach”. This is so at least since civil rights groups and individuals have appealed to courts arguing that NBS programs are unconstitutional and violatory of human rights (Couzin-Frankel 2009; Laurie 2002). Rulings at the level of constitutional and human rights are clearly a matter of “comprehensive deliberation” at the most fundamental levels of value judgments in society.

In addition to the descriptive problem of social epistemologies and the normative challenge of the discursive dilemma, another pitfall of legitimization is lack of proper awareness.

The gap in awareness might be found at the level of public participation, individual choice or both. We refer to it as the “saliency problem”.²¹ Even when the public shares the same epistemic and normative paradigms, a shift in saliency may alter the support and even tolerance of a practice. The 2000 Enschede firework disaster is a case in point. When the private bio-banking company suggested the use of NBS samples for the identification of the remains of a child victim, a public outcry ensued. Although it was not possible to maintain that the bio-banking policy was “illegitimate”, it was not even secret, people were not *sufficiently* aware of the storage of their babies’ blood samples and its potential uses. Only following this episode, did the government set detailed guidelines regarding consent to storage of NBS samples. The fire incident rendered storage of NBS sample a salient public issue.

It follows that ethical legitimization depends on policy makers’ capacity to frame questions and posit them before mindful citizens. Put in other words, public participation is not just a matter of gathering experts and stakeholders, presenting them with a regulative question and waiting for the outcome. Not every form of public participation and individual frames of choice effectively bite into the ethical issues at hand.

In her seminal typology “A ladder of citizen participation”, Sherry Arnstein observes that “participation without redistribution of power is an empty and frustrating process” (Arnstein 1969). In a similar vein, Iain Ferguson distinguishes between “deep” and “shallow” personalization of public services (Ferguson 2007). While deep personalization empowers

²¹ The concept of saliency originates in social psychology. Whereas people are aware of numerous issues, only a few are present in the forefront of people’s consciousness. Each kind of choice requires a different level of saliency. Consent to a blood test is different from consent to surgery.

individuals to contribute to the design and governance of public services as well as to make substantial personal choices in the use of these services, shallow personalization is typically unidirectional (e.g. increased access to information about the service without opening to effective feedback) and peripheral to the essence of the service (e.g. friendly interfaces, long office hours). Consequently, high rates of compliance and reduced public opposition do not necessarily indicate genuine legitimacy. This is so because participation might be shallow, people are superficially alert to the moral problems involved; they also might not see alternatives to conformity.

A proposed scheme for public participation in the design and oversight of NBS

In the previous section we argued that lack of structuring of both “public participation” and “informed consent” (or any of their variants) is the main reason why by their own admission democratic jurisdictions have failed so far to reach a satisfying regulation of NBS. In this section we lay out a scheme of public participation and informed consent that may address the difficulties discussed. Our proposed scheme relies on the following assumptions.

1. First is the assumption that discrete regulatory domains (e.g. programming newborn screening) must be couched in the broader overlapping frameworks of democratic governance (e.g. regulation of genetic information, child’s welfare, and health care economics).
2. All of these regulative domains are committed to the fundamental value of human dignity and to human rights.
3. The scheme must be open to feedback and inviting revisions, since both characterize democratic governance and public legitimization (Tilly 2004, 35; Daniels 2000).

4. The scheme does not preclude diversity in regulation. Uniformity and harmony need not be manifested in each and every detail, but loci of diversity (e.g. certain jurisdictions screen for different number of conditions than others) must be accounted for by both deliberative participation and bioethical reasoning.
5. From its very first step, programming must be based on proper formal processes (i.e. deliberative participation) as well as substantial reason-giving (i.e. accountability by certain kind of arguments).
6. The scheme acknowledges the role of expertise as the defining feature of the service (e.g. medical service). This means, at the least, that expert authority has the power to exclude contentions and intentions that are scientifically untenable.
7. Once a choice is acknowledge in one domain (e.g. choice of home-birth), society is bounded to make considerable efforts to protect the choice from being constrained by another domain. Because it is possible to meet the goals of screening without storage of the baby's data, and because such storage is considered value-laden, parents should have the power to participate in NBS without the retention of data.

The following scheme is not a detailed program, though; and it does not predicate answers to key ethical issues. It frames and steers deliberation by combining public health with clinical ethics in a manner that ultimately empowers patients' choices. Put in other words, individual choice will not be construed as dissenting with the program but as integral to its excellence.

In order to achieve this goal, we may borrow from clinical medicine a centrifuge outline of services. The outline highlights a qualitative and gradual shift from services that almost every person considers essential, to those that are most problematic or uncertain.

At the core of the outline are emergency, lifesaving and low risk/low burden practices such as control of grand mal seizure. Consent is presumed and personal choice is typically limited. Society is expected to deliver these services unconditionally (the “rule of rescue”).

In the second circle we find evidence based care whose value to the health of the person is substantial. Typical examples would be investigation of anemia and control of hypertension. In the care for these conditions, healthcare professionals have the duty to be directive when seeking consent from their patients. Rejection of care by a competent patient is tolerated as a negative liberty. When parents and guardians decline to consent to such care, doctors feel obliged to present the case before an ethics committee or judge.

In the third tier we find optional interventions whose overall value is far from established. Care givers are expected to present such options to patients, but to remain relatively non-directive. When patients refuse such care, their caregivers reassure them that their choice is neither exceptional nor deviant.

Outside the scope of clinical care, we find medical research, which, by definition, is not designed in the benefit of the individual participants. It is also subjected to a third party oversight (i.e. IRB) and cannot involve significant risk and burden relative to the existing treatment options. The specific and distinct informed consent to research informs the participants about their right to receive standard care even if they refuse participation or leave research later on.

Typically, not only does consent to a procedure capture all key steps and aspects of the procedure, but an option to “opt out” from some such aspects is not acceptable. For example, consent to a blood test may not tolerate refusal to the use of samples for quality control. Such a choice would entail either the immoral “free-rider” attitude (i.e. quality of one’s own test be controlled by other’s samples) or mere futility (i.e. testing without quality control is scientifically

invalid). Another example might be a patient request to test only to IgM antibodies against hepatitis virus, but not to test for IgG antibodies. Although it might be technically feasible and it might be possible to draw some inferences from the results, such idiosyncratic mode of testing is not recognized by medicine as a reasonable action. Obviously, if a patient comes with such an unusual request, he or she will be listened to. But, typically, medical services come in “packages”. One may consent to testing for Hepatitis B Virus but not to HIV; but there is no meaning in consent to part of the Hepatitis B Virus or HIV panel. In the same vein, a patient who consents to surgery, does not need to give consent to the surgeon’s every movement. Only value laden and distinctly risky steps require specific expressions of consent. Public participation cannot plan surgery; but it is essential to the identification and delineation of the “value” and “risk” in question.

With such understandings in mind, it might be possible to cut the pie of “newborn screening” into slices that are informed consent relevant – each piece will need its own calibration of policy on consent. This division into categories will frame public deliberation and highlight the most relevant normative questions.

For the first slice, public participation in NBS programming should help delineate core conditions whose speedy detection is considered life-saving. This kind of information is highly expert dependent. Public participation is relevant to deciding whether such testing is mandatory or only nearly so (e.g. tolerance of opting-out v. tolerance of opting-out only with certain justifications or with an ethics committee’s involvement). Screening to PKU and hypothyroidism may fall in this category.

A second slice of conditions will be considered as bearing substantial medical benefit. Expert consensus should obtain regarding this classification by “evidence based” standards; the

public should agree about the overall categorization of the tests as “substantially beneficial”, “highly recommended”, in line with “the overall good of the child” and similar categories. Often, test results are expressed in terms of likelihood, such as “sixty percent chances of developing a serious disease within three years”. Precisely on this point the public is expected to deliberate the categorization of such a test in terms of public service (e.g. whether and how to offer it) and consumer choice (the kind of information given and the framing of consent/dissent). However, because refusal to screen involves a very low risk to the baby, it is not unreasonable to tolerate parental refusal.

A third slice would be comprised of additional screening tests. Here, the experts and the public make sure that there is some scientific basis for testing and that the overall balance of benefit/burden is proportionate for tested babies, affected individuals, family and society as a whole. There is a genuine kernel of promise in these panels; but either expert or public opinion is undecided regarding the overall desirability of testing.

Clinical research in NBS should be governed like any other research in pediatrics, including IRB approval and dedicated informed consent. Owing to the universality of NBS, research on blood samples and data may set stricter standards of public participation and governance relative to the standards of research on ordinary tissue and data banking. The intensely debated conceptual transition from research on individuals’ tissues and data to “population research” on anonymized samples is emblematic of the hybrid nature of NBS as both public health and clinical enterprise.

With this conceptual framework in mind, it might be possible to propose a step-wise process for public participation.

1. On the basis of scientific knowledge and technological capacity, experts propose a NBS panel. At this phase public participation is indirect, usually by means of representative bodies (e.g. parliamentary committees) that exercise power over speeding up and incorporating novel technologies in terms of licensure and funding.

2. Mixed panels (professionals and lay participants) will then translate technological competence and scientific knowledge into medical services in ways that address the public's concerns and empower personal choice on ethically relevant aspects of the service. These panels will delineate the scope of saliency, the issues affected, even indirectly, but importantly, by the service. The mixed panels will cut the pie of NBS, in line with the slices described above. Precisely because the boundaries between the "normal" and the "pathological" are culturally constructed, as well as the notion of "benefit to the child" and similar value laden concepts, analytic-deliberative processes may help scientists working on applied tests and programs to delineate categories, select conditions to focus on, and set laboratory "cut-offs" so as to meet social perceptions of risk and value (Douglas 2009, ch. 8 following National Research Council's report *Understanding Risk* and the Presidential/Congressional Commission on Risk Assessment and Risk Management Report). For example, such panels may decide that certain conditions must be detected even at the price of high rate of false positives while other conditions are too rare or less devastating so as to justify the setting of lab standards at very high sensitivity threshold. Another example might be borderline values, which the public might refuse to classify as pathologies subjected to testing, and set high the threshold of diagnosis. A third example is whether and how to represent the possibility to screen for late-onset and poorly understood conditions (e.g. Krabbe disease, which may

erupt either in infancy or in adulthood and may be treated only by means of bone marrow transplantation). Even if these panels decide that public policy remain silent on these conditions, researchers might still obtain ad-hoc permissions to offer pilot screening programs, whose outcome might impact future revisions of NBS policies.

3. The service and its structurally independent governance will include instruments for public education, as well as evaluation and feedback from the public and its users (e.g. website, publicity officers) (AAP Newborn Screening Task Force 2000). Public education without patient empowerment is ethically shallow. But public education can serve as template for patient citizen empowerment at the public domain and patient empowerment in the sphere of private healthcare choices.

The translation of public health policy to clinical practice: a possible guideline

In the context of NBS, we may expect the healthcare team to present NBS to birthing mothers as a core service without even mentioning the possibility of opting out (e.g. PKU), as is the practice with other routine neonatal care, such as vaccination against HBV and administration of vitamin K (see Committee on Fetus and Newborn 2003). Since non-compliance with NBS poses a low risk to the neonate (less than 1/1000), and since the procedure involves invasion – however minor – into the body and some aspects of privacy (which are not the case in compulsory use of safety belts and car-seats), justification of compulsory screening must be consistent with the power of parents to expose their children to risk in other contexts. A healthcare professional will inform the mother (or parents) about the recommendation to screen for additional conditions, and may also propose experimental screening to which informed consent may be given, and payment

may be sought. Mothers would be asked whether they wish that secondary information be communicated to them, and whether they consent to storage and research.

Suppose that the mixed panel decided not to actively disclose certain incidental findings to individuals. But when these individuals become exposed to efficient public education, they will learn about the possibility of incidental findings and will be able to retrieve them upon request. Such a choice will constitute revisibility of a default policy at the level of the consumer. In case many such individuals request the incidental information, the public panels may have a reason to revise the policy overall (revisibility of the policy). In such a manner a public health policy is uniform, yet non-constraining; it empowers personal choice rather than mute it.

In sum, public participation and informed consent are key regulative instruments whose chief role is the empowerment of people (especially stakeholders) and the respect for personal choices. But there are many ways to conduct participation, and structure an informed consent. Both methods are liable to error, bias and widespread dissatisfaction. NBS poses a special challenge to regulation because it fits neatly neither public health nor clinical care.

Drawing on research on public participation and personalization of public services, we have offered a scheme for public participation in NBS in a manner that fleshes out its dual character as both a public health enterprise and a clinical service. The scheme ensures that value-laden issues be placed at the heart of deliberation and that the policy includes spaces for individual choices regarding these value laden aspects. Lastly, public bodies as well as the cumulative effect of individual choices will have the power to contribute to the ongoing governance and revision of the policy.

CONCLUSIONS

The scientists and professionals who are responsible for NBS programs behold it as a discrete activity. NBS is construed as a universal, cheap, pain-free and risk-free intervention that is the only an effective means to save many babies from serious morbidity, disability and even mortality. This simple scheme renders NBS as a straightforwardly beneficial service, suitable to every society and environment that can afford it.

Exploration of the history of NBS and the literature about it in the West, and targeted focus on Israel have revealed a quite different and complex picture. Although for over 95% of neonates NBS means a tiny prick only, the NBS system has bolstered the practice of hospital birth and set its duration, becoming at the same time an instrument for and an inherent part of the policy of healthy child-birth. This role of NBS has substantial implications on the birth-related choices and experiences of almost all mothers, being an almost universal practice in any western maternity ward. It bears a considerable impact on public moneys, since the implications of testing fall beyond its direct measurement. The NBS system also creates a significant number of babies and families who suffer from doubt, unnecessary procedures and other physical and psychological burdens, such as the “false-positive patients” and “patients in waiting”. Moreover, the universalization of NBS and its increased reliance on MS/MS and information technologies affect the privacy of every person, his or her immediate family members and even relatives of screened babies-

The promise of complete prevention of serious medical problems has clearly been fulfilled regarding some conditions, mainly those that had been screened for before the era of expanded NBS – PKU and hypothyroidism. But many other conditions screened in Israel and in many other jurisdictions are not fully preventable or effectively treatable.

Behind these complications we have found that the search for harmonization poses its own challenges. While harmonization as standardization is more than welcome at the international level, so that different programs may be able to integrate their systems with laboratory standards shared by most countries, when harmonization is interpreted as universalization, issues of distribution of resources arise. In fact, the attempt to extend NBS to each and every neonate is clearly not cost effective at least in terms of marginal returns. Nevertheless early pilots aimed at children at risk only, or those based on opting-in ambulatory services were abandoned. Thus, the overall, benefit of NBS is presented against one alternative – no screening at all; but there is no structured analysis of the benefit / burden balance of universal, quasi mandatory expanded panel relative to alternatives of “softer” programs, such as programs focusing on core-conditions (double tired), elective ambulatory testing and the like.

This research has traced roots of this universal ethos of NBS to the “rule of rescue” and its social construction as a “life-saving” intervention. In the face of an individual whose life is in danger, direct action should be performed in order to save him or her, with no regard to external considerations. Life has no price. From that moment on, every part of NBS has been virtually incorporated in the scheme of “rescue”. Even critics that advocated limits on NBS, has referred to it as a uniform practice of rescue, whose margins need demarcation. Even when NBS has been expanding by leaps and bounds and clearly stretching the limits of the law, very few bodies have tried to stratify NBS into components whose urgency and legitimacy vary. .

The social construction of NBS as rescue has been traced to the 1960s in the United States. At the time, other aspects of child health were medicalized, such as child abuse, responsibility for “retarded” children was declared a presidential concern, and breakthrough in genomics (mainly karyotyping) enthralled professionals and the public by the promise of

diagnosing and then preventing hitherto mysterious and intractable inborn conditions such as Down Syndrome and Turner Syndrome. Patients advocacy groups have contributed significantly to the emergence of NBS as a public health service and to the pressure of rendering NBS a uniform and universal service, especially in the USA.

These groups have been conspicuously absent from the Israeli scene. However, Israel has a unique record of successful public health and healthcare services policies aimed at neonates and babies. Even when Israel was poor and developing, the United States' standards of care were the source of emulation.

The Israeli template of universal and effective pediatric care is comprised of its special legal and administrative coverage of hospital birth and "Drop-of-Milk" clinics. The Israeli expansion of NBS took place as a top-down process, with no public involvement. Nevertheless, it took lessons from other already expanded programs, paying attention to avoid public complains by making significant efforts at being user-friendly and respecting the parental right to refuse testing. Therefore, formally speaking, this is not a mandatory program. But the friendliness has been found to be "shallow" in terms of personalization of services, and the official opening for dissent contains its own inherent contradiction. For, if indeed NBS is a kind of rescue, there should not be any recognized right to refuse. But if it is indeed a "recommended" medical practice only, as the official dissent form indicates, then, the universal application and its background ethos are called into question.

The Jewish religion has supported compliance with healthcare and health lifestyles, but not active searches for hidden and incipient problems. Nevertheless, the early successes of public health and the secular and socialist Zionist ethos have made NBS and other fundamentals of pediatrics public health (e.g. vaccination, periodical check-ups) established practices. Only tiny

pockets of religious sentiments combined with New-Age sensibilities harbor hostility to vaccination, and even less so, to NBS.

The overall “Israeli mentality” (to the extent that such a generalization can be made) combines elements from the Jewish tradition and the secular, socialist and Zionist movement. Central to both is the fundamental commitment to the safety of every single community member. This national ethos of safety seems to have spread from security from persecution and other external adversities to security from devastating illness. Indeed the Israeli NBS service has mobilized all relevant arms of the state in approaching affected neonates as a matter of national emergency. With the aid of the ministry of interior census, local public health offices, police and other bodies, the NBS team traces out virtually every positively screened neonate, no matter how remote he or she might be. The narratives and perceptions of the NBS professionals about their work reflects this ethos, as well as a high sense of personal commitment for the overall success of the program. Perhaps owing to the relatively limited number of people involved, every “case” becomes a “personal mission”. They perceive every unscreened neonate as a lost child in great peril.

Perhaps this shared view can explain also the findings coming from interviewed home-birth midwives who are “outside” mainstream of child-birth; but nevertheless revert to the ethos of children’s safety when NBS is discussed. Their “alternative” and “natural” approach seems to stop once childbirth has been completed. They refer to NBS as a matter of “pathology” and “abnormality” that belongs to the realm of professionals. Once childbirth is over, they default to the mainstream track of security governed by “authoritative experts”. Their “natural” approach does not extend from childbirth to post-natal care. Therefore they do not engage in the search for alternative modes of coping with the challenge of very rare inborn conditions.

This study have found NBS systems as a hybrid of public health and clinical medicine. Complicating this mixture is the “rescue” attitude of the clinical side and the highly sensitive genomics aspects of the public one. The elaborate structure of patient (i.e. parent) information in the Israeli law and NBS service betrays an attempt to reconcile a quasi-mandatory universal public-health intervention with the emergent laws on patients’ rights, their dignity as private individuals and their power to choose when complex decisions are at stake.

The ongoing attempts to revise the Israeli Genetic Information Law in ways that accommodate NBS, posit the question whether Israel would be the first country to sanction the application of genomics to NBS by means of primary legislation. If the revision passes, NBS will be the only activity exempted from full informed consent (opting-in) and from the application of “clear and immediate benefit to the child” in the use of genetic tests.

These findings and insights are particularly interesting so long as NBS is offered universally only as a uniform service (i.e. no option of consenting to only some tests or to tests without storage) with a weak opting-out structure. Time will tell to what extent the public and the bioethics community may find adequate the unique Israeli attempt to balance these difficulties by means of extensive efforts at patient-information. NBS advocates indicate that the actual rescue of a few babies would justify the economic, moral and legal “costs” of NBS. For them, the fact that these few babies are a tiny fraction of the dozens of thousands does not matter much, as long as these few are real, and their reality is brought into light by the centralization of the Israeli NBS services. For the NBS people and for the families of these children, that’s worth the whole world.

APPENDICES

1. From the official Israeli brochure: Information for a woman that is going to give birth

Information for a woman that is going to give birth

Including screening tests for healthy newborn.

Topics of discussion:

- Pain control at birth
- What is episiotomy
- The medical follow-up after birth
- The feeding of the newborn
- Smoking
- Physical exam of a newborn by a physician
- Treatment
 - Vitamin K
 - Eye drops
- Vaccination
 - Hepatitis B

On newborn screening

Most children are born healthy but should undergo additional tests because some of the children that look healthy upon birth are actually affected by severe diseases.

Early detection of the disease may prevent serious complications and severe retardation.

Timing of the exam.

Prior to discharge of the baby from the hospital, a small sample of blood is taken by means of a prick in the heel. This should be done at least 36 hours after birth. This sample is sent to the central laboratory located in Tel Ha Shomer.

Results.

Immediately following abnormal results, the parents are been called directly through the number given in the hospital in order to perform a repeated test and to initiate treatment in case this is necessary.

The performance of repeated test.

Sometimes is not possible to carry out the test or to arrive at conclusions, and this is due to reason unrelated to the disease. For example, the test was taken too early; the quantity of blood was not sufficient; the quality of the sample was not good; there is a suspicion of a mild medical condition.

In such cases there is a need to retest.

Invitation to repeat a test does not hint that the baby has been diagnosed as sick.

The repeated test is carried out by means of tipat halav in the area following the address given in the hospital.

It is possible to get more details through the caring team and in the web site of the Ministry of Health.

www.health.gov.il/genetics

Assistance in the process.

It is possible to help by leaving details information in the registration office: the precise address and the telephone number where by means it is possible to contact the mother in the days and weeks following the discharge of the hospital.

DISEASES TESTED IN ISRAEL

Phenylketonuria

It is a heritable disease that harms the normal development of the brain. Early detection facilitates treatment (mainly nutritional) that prevents the appearance of the signs of the disease.

In Israel ten sic babies are diagnosed every year (1:50.000 births). These children receive special dietetic treatment that does not contain phenylalanine and they are being followed by the national center in Sheba Hospital.

Children that receive appropriate early treatment develop like normal children in every measure.

Congenital Hypothyroidism

Deficiency in the thyroid hormone might cause severe damages in the newborn which is in the process of rapid growth. Hence, every baby with low level of hormone will be referred to an endocrinologist for completion of diagnosis and for treatment (this is the missing hormone if necessary). In Israel. 60 to 70 babies a year are discovered (1:3.000 births). These children receive a treatment (the missing hormone) for all their lives and are followed by their primary care physician.

Children that receive appropriate early treatment develop like normal children in every measure.

Over activity of the adrenal gland (CAH) Congenital Adrenal Hyperplasia.

It is an inherited disease which is relatively common in the Israeli population. Some of the affected children may develop waist of salts that may be life threatening.

Additional metabolic diseases.

There are many hereditary diseases that are caused by inborn defects and signs do not yet appear in the very first days of life. In some of these diseases, early detection and appropriate treatment may improve the developmental conditions of the neonate. A committee consulting the Ministry of Health determines on the basis of local and international knowledge, which diseases should be checked. More details on the web site

www.health.gov.il/genetics

What is done with the samples when the exams are over

After the performance of the tests and the arrival of the results, it is possible that the samples may be use for quality control.

Is it possible not to perform the tests.

Yes. If the parents refuse the proposed tests, they have to tell it to the doctor responsible for the neonates and sign a form of refusal after they receive explanation about the implication of no testing.

- Social security financial support
- General counseling related to the new baby
- The safety chair in the car
- The follow up in Tipat Halav

2. Israeli homebirth ordinance

(Translation: Sharon Neeman)

Circular No.: 17/2012

Jerusalem, 3 Sivan 5772

May 24, 2012

File No.: 4/1/14

To: Directors of General Hospitals
 Directors of Departments of Obstetrics and Gynecology
 Delivery room charge nurses
 Directors of Department of Neonatology and Neonatal Special Care
 Directors of Medical Divisions – Health Maintenance Organizations
 Chair, Israel Organization of Midwives
 Chair, Organization of Home Delivery Midwives

Re: Home deliveries

Ref.: Circular No. 1/2008 dated January 21, 2008

Attached hereto is an updated version of our above-referenced circular, which replaces and cancels it.

This circular refers to male and female obstetricians (hereinafter: “Doctor”) and to male and female midwives (hereinafter: “Midwife”).

General:

The Ministry of Health respects every woman's right and freedom to choose where she will give birth. At the same time, as the entity in charge of public health, the Ministry believes it is its professional and moral duty to emphasize that deliveries in recognized and authorized delivery rooms are safer for mother and baby alike.

In light of the fact that home deliveries are performed in Israel, following are guidelines for the performance thereof, which establish a balance between the expectant mother's freedom of choice and the need to protect her safety and that of her baby (who does not benefit from the freedom of choice).

Definition:

"Home Delivery" – giving birth in the mother's home, following advance planning and preparation and based on the mother's choice.

Pursuant to the Midwives' Ordinance, 1929 and the Doctors' Ordinance (New Version), 5737-1976, a registered Midwife or a Doctor is entitled to perform a Home Delivery in the mother's home.

We hereby clarify that it is not prohibited for a woman to give birth in her home without the assistance of a professional. However, it is prohibited for anyone who is not a Midwife or a Doctor to engage in the occupation of delivering babies.

The operation of a place which is intended as a delivery room, other than within an authorized medical institution, is prohibited.

1. **Definition of the persons who are authorized to perform Home Deliveries**

- 1.1 Only the following persons are authorized to engage in the occupation of performing Home Deliveries:
- a. A Midwife who is registered in the Midwives' Ledger in Israel, who has three years' seniority working in a delivery room which is recognized in Israel, pursuant to the National Health Regulations, after having acquired experience in 10 Home Deliveries at which an experienced Home Delivery Midwife was present.
 - b. A Doctor who is a specialist in Obstetrics and Gynecology, who holds a license and a specialist's certificate in Israel, and who has engaged in the occupation of obstetrics in the delivery room which is recognized in Israel for three years (hereinafter: the "Doctor").
- 1.2 Anyone who engages in the occupation of performing Home Deliveries must have taken a course in resuscitation, at the level of at least BLS, including an NRP (Neonatal Resuscitation Program) course which is offered by the Israel Neonatal Society, and is required to keep the certificate which attests to having taken the course. After taking the courses, one refresher course per year must be taken.
- 1.3 Persons who engage in the occupation of performing Home Deliveries must maintain updated knowledge, on an ongoing basis, of the relevant guidelines and circulars on the Israel Ministry of Health Website – www.health.gov.il.
- 1.4 Any person who engages in the occupation of performing Home Deliveries should be insured under a professional liability insurance policy.

If the person performing the Home Delivery is not insured as set forth above, it is his/her duty and responsibility to inform the expectant mother of this fact in a timely manner, to explain the implications of not having insurance, to ensure that the expectant mother has understood and consents, and to document having done so.

2. **Necessary conditions for the performance of Home Deliveries**

Following is a detailed listing of the conditions which constitute a precondition for the advance planning and performance of Home Deliveries:

2.1 **Obstetrical and physical conditions:**

- 2.1.1 Pregnancy with a single fetus in cephalic ("head first") presentation.
- 2.1.2 Delivery in week 37 to week 42 of pregnancy.

Starting in week 41 (40+6) of pregnancy, a normal biophysical score must be ascertained no later than three days prior to the delivery.

- 2.1.3 Fetal weight estimated between 2500 and 4000 g.
 - 2.1.4 The expectant mother must provide a declaration of her state of health. If the Midwife has any doubt that the expectant mother's health will allow her to withstand a Home Delivery (as set forth below), a certificate to that effect must be requested from the attending physician.
 - 2.1.5 The expectant mother is over 18 years old (if she is between 17 and 18 years old, her parents' written and signed consent must be obtained), legally competent and able to make a decision independently and of her own free will.
 - 2.1.6 Written documentation of the expectant mother's medical and obstetrical history exists.
 - 2.1.7 Documentation shows that the present pregnancy has been monitored by a Doctor and a Midwife in accordance with the Ministry of Health guidelines.
 - 2.1.8 Documentation shows that a prenatal ultrasound examination was performed in the course of the pregnancy.
 - 2.1.9 Documentation shows that gestational diabetes has been ruled out.
- 2.2 Conditions in the environment of the expectant mother:
- 2.2.1 It must be ascertained in advance that the expectant mother's home is suitable for a Home Delivery – that it is clean and has hot running water, electrical power, heat and a telephone.
 - 2.2.2 It must be ascertained that the room in the expectant mother's home which is slated to be used for the Home Delivery is suitable in size for the required activity (not less than 10 m²).
 - 2.2.3 It must be possible to arrive at a hospital which has a certified delivery room within 30 minutes after making the decision to transfer to the hospital.
- 2.3 Informed consent:
- The expectant mother's informed consent in writing must be obtained, on an "Application and Consent by the Mother for a Home Delivery" form (Appendix A), after the attending Midwife / Doctor has provided a detailed explanation, which includes at least all of the information which is included in the aforesaid form.
- 2.4 Instrumentation and equipment required for a Home Delivery:

- 2.4.1 Home Delivery kit (at least 4 large OB pads).
- 2.4.2 Cord cutting kit (2 clamps, scissors, Kocher's forceps, bandages).
- 2.4.3 Sterile suture kit.
- 2.4.4 Disposable sterile gloves.
- 2.4.5 Amniotome.
- 2.4.6 Fetal Doppler.
- 2.4.7 Mobile suction device and ancillary equipment including catheters for mother and baby, or oral suction device.
- 2.4.8 Airway for mother and baby.
- 2.4.9 Ambu bag and mask for mother and baby.
- 2.4.10 Oxygen and ancillary equipment.
- 2.4.11 Sphygmomanometer.
- 2.4.12 Adult urinary catheter.
- 2.4.13 Infusion set and ancillary equipment for the mother.
- 2.4.14 Fluids and solutions for infusion.
- 2.4.15 Drugs: Uterine contractors (such as oxytocin, methergine)
 Adrenaline
 Eye ointment / drops (whichever is customarily used in Israel)
 Vitamin K
- 2.4.16 Alcohol.
- 2.4.17 Sterile pads.
- 2.4.18 Syringes and needles for injection.
- 2.4.19 Scissors.
- 2.4.20 Test tubes for blood tests.
- 2.4.21 Baby weighing scale.
- 2.4.22 Thermometer.

3. Contraindications for the performance of Home Deliveries

- 3.1 If, in light of the medical information which the expectant mother provided or which is set forth in her medical records, there is any doubt that the state of her health will allow her to withstand a Home Delivery, she must be required to present a certificate of approval from her attending physician as a prerequisite for the performance of the Home Delivery.

A certificate of approval from the attending physician is always required in the following situations:

- 3.1.1 Chronic diseases and handicaps which are likely to affect the course of the delivery and/or the newborn.
- 3.1.2 An active infectious disease in the expectant mother.
- 3.2 A Home Delivery must not be performed if the expectant mother uses drugs or drug detox medications.
- 3.3 Complications in the expectant mother's obstetrical history which contraindicate a Home Delivery. A Home Delivery must not be performed if any of the following occurred in previous pregnancies:
- 3.3.1 Prenatal or perinatal fetal death due to a known obstetrical reason which is likely to affect the course of the present pregnancy or of the delivery.
- 3.3.2 Placenta previa other than due to trauma.
- 3.3.3 Shoulder dystocia at birth.
- 3.3.4 Grade 3-4 tear in the perineum or tear in the cervix.
- 3.3.5 Postpartum hemorrhage.
- 3.3.6 Previous newborn who developed early-onset GBS disease.
- 3.4 Congenital or acquired defects of the uterus or birth canal which contraindicate a Home Delivery. A Home Delivery must not be performed if any of the following exist:
- 3.4.1 Unicornuate or bicornuate uterus, uterus with septum, double uterus, double vagina, vagina with septum, uterus with large myoma or myoma presenting as tumor previa in the present pregnancy, all according to the obstetrical history and the medical documentation.
- 3.4.2 Surgical scar in the uterus [cesarean section, myomectomy, trauma and puncture], S/P separation of intrauterine adhesions.
- 3.4.3 Congenital or acquired deformation of the pelvis or spine.

- 3.5 Problems with the present pregnancy which contraindicate a Home Delivery. A Home Delivery must not be performed if any of the following exist:
- 3.5.1 Pregnancy with more than one fetus.
 - 3.5.2 Any presentation other than cephalic (“head first”) presentation.
 - 3.5.3 Chronic or acute systemic diseases which were diagnosed during the pregnancy, including heart diseases, diabetes (including gestational diabetes), and autoimmune and thrombophilic diseases.
 - 3.5.4 Hypertension.
 - 3.5.5 Nephritis or infection of the urinary tract which does not respond to antibiotics treatment in the course of the pregnancy.
 - 3.5.6 GBS bacteriuria in the course of the pregnancy.
 - 3.5.6 Deep venous thrombosis (DVT).
 - 3.5.7 Morbid obesity toward the expected date of birth.
 - 3.5.8 Maternal anemia in the present pregnancy (HGB <10 g/dl), thrombocytopenia (<100,000/ μ l), according to a recent blood count within the two weeks before birth, and/or other congenital or acquired disorders of the blood clotting mechanism, including treatment with anticoagulants in the present pregnancy.
 - 3.5.9 Infection in pregnancy – fetal infection (or substantiated suspicion), positive torch test, or carrier status of infectious diseases such as genital herpes, HIV, GBS, hepatitis B or C.
 - 3.5.10 Signs leading to a suspicion of toxemia.
 - 3.5.11 Cervical suture which has not yet been removed.
 - 3.5.12 Known state of Rh factor sensitization.
 - 3.5.13 Bleeding of uterine origin in the second or third trimester.
 - 3.5.14 Pregnancy in which a prenatal ultrasound examination was not performed and gestational diabetes was not ruled out.
 - 3.5.15 Suspicion of a defect which is likely to cause an immediate functional disorder in the newborn.
 - 3.5.16 Fetal arrhythmia or other pathological fetal pulse pattern immediately before birth.

- 3.5.17 Intrauterine growth restriction (IUGR).
- 3.5.18 Estimated weight of the fetus immediately before birth – >4000 g or <2500 g.
- 3.5.19 Complete or partial placenta previa or low-lying placenta.
- 3.5.20 Polyhydramnios and oligohydramnios.
- 3.5.21 Decreased fetal movement.
- 3.5.22 Maternal temperature of 37.8°C or higher immediately before birth.

4. **Rules for treatment of the mother and the newborn, record-keeping and reporting**

Treatment of the mother and the newborn before, during and after the birth will be carried out in accordance with the Ministry of Health guidelines and the provisions of applicable law.

- 4.1 The Midwife / Doctor will instruct the expectant mother in a timely manner with respect to signs of active birth.
- 4.2 The Midwife / Doctor will arrive at the expectant mother's home within one hour after she gives notice that signs of active birth have appeared.
- 4.3 The Midwife / Doctor will remain with the expectant mother from the beginning of the active birth and for at least two hours after the birth is complete.
- 4.4 The expectant mother's vital signs must be monitored at least once an hour.
- 4.5 The fetal heartbeat must be monitored at least once every half hour in the first stage of the birth and every 5-10 minutes in the second stage.
- 4.6 The newborn must be examined and his/her condition must be evaluated immediately after the birth.
- 4.7 The Midwife / Doctor will perform close supervision and monitoring of the newborn for a period of at least two hours after the birth.
- 4.8 The Midwife / Doctor must make a repeat visit to the new mother, 24 hours after the birth.
- 4.9 The Midwife / Doctor will provide the new mother with information on how to contact them during the postpartum period.
- 4.10 **Recording and summarizing the course of the delivery:**
 - 4.10.1 The Midwife / Doctor will keep an archive arranged according to the laws and regulations, for documentation of the Home Deliveries performed by them.

- 4.10.2 It is necessary to perform proper documentation of the information which was given to the mother, vital signs, the fetal heartbeat, the findings of the examination of the newborn and the course of the delivery – both during and immediately after the delivery, as is customary and required for any medical record.
- 4.10.3 The record-keeping must include:
- A record of the course of the delivery, including data on the maternal and fetal monitoring performed during the delivery.
- A summary of the course of the delivery (Appendix B).
- A record of the physical assessment of the newborn (Appendix C).
- 4.10.4 A copy of each record and report as set forth above should be given to the mother, and the original must be kept by the Midwife / Doctor.
- 4.10.5 The minimum period of time during which the reports and the accompanying forms must be retained by the Midwife is 25 years (at least).
- 4.10.6 The documents must be legible and available for inspection by the Ministry of Health, when such an inspection is performed.
- 4.11 Upon the conclusion of a Home Delivery with no complications, the new mother must be informed that, within 24 hours after the birth, the newborn must be examined by a pediatrician. The new mother must be encouraged to go to a hospital so that she and the newborn can be examined and the newborn can be registered properly within 24 hours after his/her birth.

5. **Rules for transferring the mother and the newborn from a Home Delivery to a hospital**

- | |
|---|
| <ul style="list-style-type: none">- In any situation involving a deviation from a normal course of delivery, and/or in which the Midwife / Doctor is not convinced that (s)he is capable and/or that it is possible to administer proper treatment in order to safeguard the health of the mother and baby, they <u>must</u> be transferred to a hospital.- A request by the mother to be transferred to a hospital, at any stage of the birth, must be honored immediately. |
|---|

The occurrence of any one of the following cases or complications is sufficient to constitute a medical indication for transferring the mother to a hospital. The Midwife / Doctor is required to inform the mother that she must be evacuated to a hospital immediately / urgently, as is relevant.

5.1 Indications for transferring a mother to a hospital in the course of the delivery

- 5.1.1 More than a normal amount of bleeding.
- 5.1.2 Signs leading to a suspicion of placental abruption: protracted pain in the lower abdomen, increased uterine tonus, changes in the fetal pulse which indicate distress, bleeding, hypotension with no external bleeding.
- 5.1.3 Overt or occult prolapse of the umbilical cord.
- 5.1.4 Significant changes in the mother's vital signs, such as:
 - a. Fever rises above 38°C in the course of the delivery.
 - b. Fast pulse <120/min for 15 minutes or more.
 - c. Drop in systolic pressure by 20 mmHg below the basic value for 15 minutes or more.
 - d. Blood pressure >140/90 in two readings, one hour apart.
- 5.1.5 Blood or meconium in the amniotic fluid during the first stage of the birth.
- 5.1.6 Pathological course of birth, such as:
 - 5.1.6.1 Arrest of dilatation for two hours during the first stage of the birth, in the presence of regular contractions.
 - 5.1.6.2 The second stage of the birth takes longer than three hours in a primipara or two hours in a multipara, provided that there is no arrest of descent.
- 5.1.7 Pathological changes in the fetal heart rate (FHR), including basic heart rate <110/min or >160/min.
- 5.1.8 Arrested development of active birth, 12 hours after the breaking of clean water. Proper hygienic conditions must be maintained and the mother must be monitored for signs of development of chorioamnionitis.
- 5.1.9 Signs of hypovolemia in the mother.

5.2 Indications for transferring a mother to a hospital after the delivery

- 5.2.1 The placenta has not emerged one hour after the emergence of the fetus.
- 5.2.2 Heavy bleeding before or after placental separation.
- 5.2.3 Incomplete placenta or suspicion of incomplete placenta.

- 5.2.4 Pathological changes in the mother's blood pressure, including a drop in systolic blood pressure by 20 mmHg below the basic value for 15 minutes or more, or blood pressure >140/90.
 - 5.2.5 Respiratory distress.
 - 5.2.6 Confusion, agitation and/or change in the state of the mother's consciousness.
 - 5.2.7 Difficulty in suturing tears or performing an episiotomy.
 - 5.2.8 Appearance of a hematoma in the birth canal or the vagina after the birth.
 - 5.2.9 Grade 3-4 tear in the perineum or the vagina, or suspected tear in the cervix.
 - 5.2.10 Pathological mental signs in the new mother.
- 5.3 Indications for transferring the newborn to a hospital immediately
- 5.3.1 Birth weight >4000 g or <2500 g.
 - 5.3.2 Signs leading to a suspicion of respiratory distress:
 - a. Number of respirations >60/min.
 - b. Chest wall retractions.
 - c. Nasal flaring and sighing.
 - d. Cyanosis or pallor.
 - 5.3.3 Hypoxia, indicated by a blue-gray skin color which improves upon the administration of oxygen and returns when the oxygen is stopped. The newborn should be transferred to hospital by ambulance with oxygen administered while traveling.
 - 5.3.4 Abnormal skin color: pale, yellow or red.
 - 5.3.5 Body temperature <35.5°C in two readings, with no attempt to warm the newborn.
 - 5.3.6 Apgar ≤7, five minutes after birth.
 - 5.3.7 Tremor, abnormal movements, convulsions.
 - 5.3.8 Signs of trauma, including signs of paralysis, subcutaneous hemorrhages.
 - 5.3.9 Birth defects.

5.4 Transferring the mother and newborn to a hospital

- 5.4.1 The method used for transferring an expectant / new mother (by ambulance or other vehicle) will be determined by the Midwife / Doctor.
- 5.4.2 Any transfer of an expectant / new mother will always be accompanied by the Midwife / Doctor.
- 5.4.3 The Midwife / Doctor must inform the charge midwife / a doctor at the maternity hospital of the transfer to the delivery room and must provide relevant medical information.
- 5.4.4 A completed "Transfer of Mother and Newborn from Home Delivery to Hospital" form (Appendix D) must be transferred along with the new mother and the newborn.
- 5.4.5 The Midwife / Doctor will provide the hospital with a verbal and written summary of all of the details related to the mother, the pregnancy, the course of the delivery and the newborn, including Appendices B, C, D.

6. **Guidelines for treatment of the new mother and the newborn after the birth (if the mother chooses not to go to a hospital within 24 hours of the birth)**

The Midwife / Doctor is responsible for the following treatment:

- 6.1 Preventive ophthalmological treatment must be given to the newborn according to the Ministry of Health guidelines.
- 6.2 The newborn must be injected with Vitamin K, at a dosage of 0.5 mg, as soon as possible after birth. If the parents refuse administration by injection, Vitamin K may be administered orally according to the following protocol:

First dose – 2 mg within six hours after birth, when the infant is able to suck.

Supplementary treatment: a dose of 2 mg at 1 week and 2 weeks of age.

If the infant spits up the vitamin within one hour of administration, repeat the dose.
- 6.3 When the mother is Rh negative or if antibodies to blood group antigens were found in the mother's serum in the past, it is necessary to determine the newborn's blood type, hemoglobin and blood bilirubin levels.
- 6.4 When the mother is Rh negative and the newborn is Rh positive, the mother must receive an Anti-D vaccine.

- 6.5 The newborn's blood must be sampled and tested for the metabolic diseases for which newborns are tested in hospitals, including phenylketonuria and thyroid functions, no earlier than 48 hours and no later than 7 days after birth, and a hearing test must be performed.
- 6.6 Instruction must be given on how to care for the newborn, including: breast-feeding, formula feeding, putting to bed (positions), diapering, washing, wiping away secretions, navel care, dressing, setting the temperature of the room according to the season, importance of buckling the baby into a car seat – in accordance with the Ministry of Health guidelines and the provisions of applicable law.
- 6.7 The new mother must be informed that an examination of the newborn by a pediatrician within 24 hours after birth is essential. Subsequently, routine monitoring of the baby will take place within a medical framework – at a well-baby clinic or by a pediatrician.
- 6.8 The new mother must be informed that, according to the Ministry of Health recommendations, the baby should be taken to a well-baby clinic for vaccination against viral hepatitis B within 24 hours after birth.
- 6.9 The new mother must be told to register the new baby at the Ministry of the Interior, along with a doctor's certificate / an affidavit pursuant to Amendment No. 9 of the Population Registry Law, which is reproduced in Ministry of Health Circular No. 3/2006, Section B.

7. **Rules for admitting the mother and the newborn from a Home Delivery to a hospital**

- 7.1 Upon admission of the mother and the newborn from a Home Delivery, a hospitalization procedure will be performed, as is customary in a delivery room. The full medical and nursing admission procedure must be carried out. A copy of the form in which the course of the delivery is recorded will be added to the medical file.
- 7.2 The mother and the newborn will be examined and receive subsequent treatment in accordance with the Ministry of Health / hospital circulars and procedures, including comprehensive testing of the newborn for metabolic diseases and a hearing test.
- 7.3 Upon the conclusion of the admission and examination process, the mother will be offered the opportunity to be hospitalized. If she refuses, she will be discharged by the senior OB/GYN on the shift.
- 7.4 As a rule, the mother and the newborn will be discharged simultaneously, other than in medical situations in which there is an indication for the newborn to remain hospitalized after the mother has been discharged (Medical Administration Circular No. 43/99).

- 7.5 If the mother refuses to allow treatment for the newborn, this should be documented in a Refusal of Treatment Form as is customary at the hospital, signed by the nurse, the pediatrician and the mother.
- 7.6 If the mother asks to be discharged early, the nurse must do the following:
- 7.6.1 Ensure that the newborn is examined by a pediatrician prior to discharge.
 - 7.6.2 Ensure receipt of a vaccination record.
 - 7.6.3 Instruct the mother / the parents as to the additional examinations which the newborn must undergo: comprehensive testing for metabolic diseases, bilirubin monitoring as necessary, and a hearing test. The responsibility for the performance of these examinations rests with the mother / the parents.
 - 7.6.4 If the mother is Rh negative, blood samples will be taken from the mother and the newborn for testing, and the mother will be asked to wait for the test results in order to receive an Anti-D vaccine if necessary.

Please forward the content of this circular to all relevant personnel in your institution.

Very truly yours,

[Signature] Prof. Arnon Afek

Head of the Medical Administration

Copies: Director-General
Vice-Director-General
Senior Deputy Director-General for Information and Computerization
Senior Deputy Director-General for Administration and Human Resources
Senior Deputy Director-General for Planning and Construction of Medical Institutions
Deputy Director-General for Health Economics
Deputy Director-General for Planning, Budgeting and Costing
Deputy Director-General for Health Maintenance Organizations
Deputy Director-General for Public and International Relations
Head of the Medical Technologies and Infrastructures Administration
Ombudsman

Ombudsman Pursuant to the State Health Insurance Law

Comptroller of the Ministry

Legal Advisor

National Head Nurse and Head of the Nursing Administration

Head of the Public Health Services

District Doctors – District Health Officers

Director of the Medical Technology Policy Division

Director of the Institution and Instrument Licensing Division

Head of the Mental Health Services

Director of the General Medicine Division

Director of the Community Medicine Division

Director of the Pharmaceutical Division

Director of the Information and Computerization Services Division

Head of the Medical Records and Information Section

Director of the National Center for Disease Control

Director of the Emergency Division

Director of the Health Professions Division

Director of the Quality Assurance Division

Director of the Internal Audit Division

National Head Psychologist

Director of the Epidemiology Division

Head of the Laboratories Department

Coordinator of National Councils

Medical Library

National Nursing Officer (General Medicine)

National Nursing Officer (Community Medicine)
National Nursing Officer (Mental Health)
National Nursing Officer (Public Health)
Head Nurse – Clalit Health Services
Medical Director, Division for Care of the Mentally Challenged – Ministry of Social Welfare
O/C, Israel Defense Forces Medical Corps
Head, Medicine Section, IDF Medical Corps HQ
O/C, Israel Prison Service Medical Corps
O/C, Israel Police Medical Corps
Director-General, Hadassah Medical Organization
Health Coordinator, Budgets Division – Ministry of Finance
Chair, Israel Medical Association
Chair, Israel Organization of Doctors in Civil Service
CEO, Medical Risk Management Company
Israel National and University Library
Israel State Archives
CEO, Inbal Company
Head of the Risk Management Department, Inbal Company

Reference No. 24863912

Medical Administration Circulars and Director-General's Circulars are published on the following Website: www.health.gov.il

Appendix A – Application and Consent by the Mother for a Home Delivery

Home delivery is intended for healthy expectant mothers who are not at risk, according to medical definitions, and who wish to give birth at home with the assistance of a licensed midwife or with the assistance of an obstetrician / gynecologist (hereinafter: the “Midwife” or the “Doctor”), without medical intervention as is customary in ordinary births in delivery rooms, under the conditions and in the environment which the expectant mother chooses.

It has been explained to me that a home delivery is managed by a Midwife or a Doctor who is competent according to law and in accordance with professional procedures.

Mother’s name: _____ Identity No.: _____

First name Last name

Father’s name: _____ Identity No.: _____

First name Last name

I, the undersigned, am hereby applying for a home delivery with the assistance of a competent Midwife or Doctor, and I hereby declare and confirm that I have received a detailed verbal explanation from the Midwife or the Doctor:

First name Last name License No.

with respect to the procedure, advantages and risks of the home delivery, including those set forth below, and I have agreed to act accordingly.

It has been explained to me that, should there be a change in my condition and/or the condition of the fetus / the newborn during or after the birth, at the discretion of the Midwife or the Doctor, transfer to a hospital will be required as quickly as possible.

It has been explained to me that, in a home delivery, the fetus will be monitored at intervals in accordance with the stages of the birth.

It has been explained to me that, in a home delivery, as in a hospital delivery, unexpected difficulties and complications which require medical intervention are likely to occur – for example: hemorrhaging (as a result of placental separation or tearing of the uterus), difficulty in extracting the fetus, and, in rare cases, clotting disorders and amniotic fluid embolism, which are life-threatening situations.

It has been explained to me that, in the situations set forth above, it is important for medical intervention to be performed rapidly, in a hospital framework, and accordingly, the transfer time to the hospital is likely to be significant for me or for the fetus / the newborn.

I am aware of the fact that a delay in medical intervention in the situations set forth above is likely to cause severe and irreversible damage to me or to the fetus / the newborn.

It has been explained to me that, in situations involving a change in my condition and/or the condition of the fetus / the newborn during or after the birth, at the discretion of the Midwife or the Doctor, it will be necessary to administer medical treatment / medication to me or to the newborn, which is not included in the natural childbirth agreement.

It has been explained to me that, in a home delivery, blood tests will be performed on me and on the newborn, and the newborn and I will receive medication which is routinely given in hospitals, with the exception of vaccinations.

It is hereby agreed that the Midwife or the Doctor will arrive at my home within one hour of the notice of appearance of signs of active birth and will remain with me throughout the entire duration of the birth and for at least two hours thereafter.

Date	Time	Expectant mother's signature
------	------	------------------------------

I hereby confirm that I have provided a verbal explanation of all that set forth above to the expectant mother, in the requisite degree of detail, and that she signed the consent form before me, after I was convinced that she had understood my explanation in its entirety.

Midwife's / Doctor's name	Midwife's / Doctor's signature
---------------------------	--------------------------------

_____ Date: _____ Time: _____

License No.

Appendix B – Home Delivery Documentation Form

I hereby declare that I performed the delivery for Ms. _____

Identity No. _____ on (date): _____

Place of birth: _____ Address: _____

The newborn baby boy / girl is healthy / other (specify): _____ Apgar at 5 minutes: ____

Birth weight: _____ Week of pregnancy: _____

Water broke at (time): _____ Spontaneously: Yes / No

Nature of amniotic fluid: Clear / Cloudy / Meconial

Duration of first stage: _____ Time of completion: _____

Duration of second stage: _____ Time of birth: _____

Duration of third stage: _____ Time of completion: _____

Describe delivery of the placenta: _____

Suction for the newborn: Yes / No

Medications which were administered during and immediately after the birth:

Mother: _____

Newborn: _____

Mother's blood pressure on conclusion of the birth: / Urination: _____

Uterus contracted: _____

Estimated quantity of maternal bleeding during the birth: _____ cc

Mother's blood type: _____ Rh: _____

Lab tests taken from the mother: Yes / No Specify: _____

Lab tests taken from the newborn: Yes / No Specify: _____

Date of birth: _____

Time of birth: _____

Midwife's / Doctor's name: _____

License No.: _____

Signature and stamp: _____

Appendix C – Physical Assessment of the Newborn

Ser. No.	Time	Organs / Variables	Normal	Abnormal
1		Skin color		Blue, yellow, red, pale, other finding
2		Respiration		Rate, nasal flaring, groaning, retraction, other finding
3		Body temperature		Temperature
4		Muscle tonus		Flaccid, excessive
5		Navel		Bleeding, open clamp, other finding
6		Anus		Closed, other finding
7		Head		Edema, wounds, birthmarks, fontanel, other findings
8		Eyes		Missing
9		ENT		Harelip/cleft palate, abnormal form/location of ear, other finding
10		Crying / Response		None, excessive, weak
11		Abdomen		Turgid, other finding
12		Back		Malformation, hairiness, hemangioma, pylonidal sinus, other finding
13		Extremities		Deformations, other finding
14		Skin		Birthmarks, wounds, blisters, other finding
15		Genitals		Hydrocele, hypospadias, enlarged clitoris, other finding
16		Other findings		

► Check the “Normal” box if finding is normal.

- ▶ Circle the word which describes the abnormal finding or describe the finding.

Date: _____

Midwife's / Doctor's name: _____

License No.: _____

Signature and stamp: _____

3. 2009 Ordinance regulating NBS in Israel

(Translated by Michael Barilan)

1. General

Screening test for early detection of PKU and hypothyroidism in neonates have been conducted in Israel for over thirty years. Early detection of these conditions enables the initiation of treatment and prevention of mental retardation. Worldwide, newborn screening programs are diverse. In most countries, screening is limited to PKU and hypothyroidism; in others the program has been expanded to cover other diseases. The kind of diseases screened and their numbers vary from country to country, thus highlighting lack of consensus in the international medical community. In Israel, an expert panel has recommended to the ministry of health that screening be expanded gradually and in line with the diseases prevalent in Israel. Hence, the lab in Sheba Medical Center has been furnished with the new equipment necessary for the expansion.

The purpose of this ordinance is to renew the guidelines regarding information to parents and the sampling of children, expedient delivery to the lab, communication of abnormal results, performance of diagnostic tests and initiation of treatment.

One must keep in mind that normal screening test does not rule out with certainty the presence of disease. Hence, in the face of clinical suspicion, the physician must rely on clinical findings and appropriate tests.

2. Information to the pregnant mother

2.1 When birth is approaching, the physician responsible for the follow up of the pregnancy, or a team member, nominated by the responsible physician, will inform the mother/parents about the screening tests and their meaning. It is possible to order the information brochure from the department of health promotion. The communication of information should be documented in the charts of the pregnancy follow up.

2.2 In case the woman has chosen home birth, it is imperative to make her sign the attached form, informing her about the importance of the tests and her responsibility for carrying them out in the right timing.

3. The responsibility for the performance of newborn screening

3.1 Proper sampling, delivery of the cards, transmission of the electronic data the NBS lab is the responsibility of the manager of the hospital where the baby has been born.

3.2 The hospital manager must take all necessary arrangements so as to assure that sampling and delivery be carried out according to this ordinance.

3.3 At planned home birth (so far as neither mother nor neonate has been hospitalized after birth), in which either a doctor or a midwife is present:

a. The physician or the midwife must inform the birthing woman (and the father, in case he is present) regarding the need to perform blood tests for PKU, hypothyroidism and other diseases, as said in this ordinance, within 48-72 hours from birth.

b. To inform the birthing woman and the father of the neonate the significance of the tests and the harm that might ensue from failure to carry them out. The physician or the midwife will inform the parents about the possibility to perform the test in all pediatric / neonatal departments in hospitals, in *Tippat Halav* (mother and child) clinics or by a physician visiting the mother at home.

c. The doctor or midwife should follow the neonate and assure with the parents that the test be done in time.

d. Responsibility for performance of the tests is the mother's/parents' and she/they must take care that blood be sampled. It is possible to perform the test in any hospital department of neonatology, *Tippat Halav* clinic, or by a physician/nurse in a home call. In case either a doctor or a nurse performs the test, their responsibility with regard to NBS is identical to the hospital manager's with regard to this ordinance. Additionally, their responsibility is even broader, since it includes responsibility for finding the child at home in case of abnormal result and for the performance of the diagnostic test.

e. The physician / midwife must document the process of information, follow up and sampling, as well as any other action done and especially document in case of refusal.

f. Whenever a newborn is registered in a hospital within 48-72 hours from birth, the hospital is responsible [for NBS]; yet, the card should be marked "not born in this hospital".

4. Performance of NBS on every live neonate

4.1 The test must be performed on every live neonate.

4.2 The head of neonatal department, or a member of the medical team s/he will nominate, will inform parents who refuse NBS on the meaning of their refusal and the consequent risks to the newborn. The parents will sign on the form "Refusal to NBS", which is attached to this ordinance. In case of refusal, an empty test card should be sent to the central lab with identification details and the words "refusal to be tested".

5. Timing of sampling

5.1 First sampling

5.1.1 Sampling of blood must be taken from every neonate in the time range of 48-72 hours post partum.

5.1.1.1 Immediately after birth the metabolites in the blood reflect [also] maternal values. Consequently, neonates younger than 48 hours must not be sampled. However, only in extraordinary cases, detailed in this ordinance, or following a written permission given in advance by the chair of the department of community genetics, might it be possible to sample 36 hours post partum.

5.1.1.2 Sampling prior to 48 hours should be carried out in case the neonate...

- Is about to undergo surgery or
- Is about to be transferred to another hospital or
- Is about to receive blood transfusion.

The reason [for early sampling] must be written on the test card.

5.1.1.3 In case of sampling from a neonate younger than 48 hours, and either not owing to the above reasons or not in compliance with this ordinance and without permission as specified in clause 5.1.1.1, the test card must be accompanied by a written explanation signed by the responsible physician, who must also sign the test card.

5.1.1.4 A neonate who was born alive, but has died before sampling, should be sampled posthumously, with the consent of the parents, and to write on the test card that the blood has been taken after death.

5.2 Second sampling

5.2.1 In addition to the first sampling, another sampling should be taken from every neonate (including premature neonates) who is hospitalized for over ten days. The second sampling should be carried out before the child is thirty days old or prior to discharge –the earliest of these events.

5.2.2. In case the baby has not been fed after birth, sampling should be taken 48 hours after the termination of the fast.

5.2.3 Whenever early sampling takes place owing to surgery and/or transfusion, a second sampling must be made. Its timing is up to the discretion of the caring physician.

5.2.4. A neonate who has been transferred from another hospital must be sampled as early as possible, but not earlier than 48 hours after birth. “Not born in this hospital” must be marked on the test card.

5.2.5 “Second sampling” should be marked on the test card.

5.3 A parturient mother who wishes to leave the hospital prior to 36 hours

5.3.1. The chief of neonatology, or a member of the caring team he has appointed, will explain to the mother the possible health implications of early discharge. She will be informed that such discharge implies a waiver of NBS. The mother/parents are requested to sign on “refusal to NBS” form, which is attached to this ordinance. The informing doctor should sign alongside. The mother will be informed about the option to perform the test in a *Tippat Halav* clinic. She will be informed about the appropriate timing as well.

6. The test card

7. Transmission of information by means of electronic media

8. Sampling the neonate

9. Delivery of test cards from the hospital to the lab

9.1 After they have dried well, the test cards will be sent on every working day to the NBS lab. Test cards must not be retained in the hospital.

9.2 The sender of the sample is responsible to ensure that the card reaches the lab:

9.2.1 The hospital will confirm directly with the lab, by means of the dedicated bidirectional lab.

9.2.2 A sender who is not a hospital will carry out the confirmation by means of the public health office.

10. The screening tests that are performed on every neonate

10.1 Normal screening test does not rule out a disease. In the face of suspicion, the caring physician should rely on the clinical findings and perform diagnostic tests.

10.2 The list of diseases screened in Israel

Phenylketonuria

Congenital hypothyroidism (Primary)

Congenital adrenal hyperplasia

Maple syrup urine disease (MSUD)

Homocystinuria

Tyrosinemia type I

Glutaric aciduria type 1

Methylmalonic academia

Propionic acidemia

Medium chain acyl-co-A dehydrogenase deficiency (MCADD)

Very long chain Acyl COA dehydrogenase deficiency (VLCADAD)

10.3 This list will be occasionally re-examined. Additional tests might be added. An updated list will be posted on the website of the department of community genetics and the lab for NBS.

11. Reporting the results and carrying out the follow-up

11.1 Reporting results

11.1.1 Normal result of the first test will be posted on the website of the lab/dept. of community genetics.

11.1.2 If, owing to technical reasons, a repeated sampling is required, the lab will contact the local public health office, which will locate the child according to the data on the test card. The local public health office is responsible, in coordination with the hospital, to perform a second sampling and to send it to the lab.

11.1.3 In case of borderline result, a functionary who has been authorized for this purpose by the dept. of community genetics, will inform the public health office [close to] the address on the test card.

11.1.3.1 If the child is not hospitalized, the public health office is responsible for repeated sampling and its delivery to the lab. If, instead of a repeated sampling a diagnostic test has been performed, the public health office is responsible for reporting the results to the NBS lab.

11.1.3.2 If the child is hospitalized, the hospital is responsible for diagnosis and follow up. If a diagnostic test has been performed, the hospital must communicate it to the NBS lab.

11.4.4 in case of an abnormal result that requires immediate referral an authorized functionary in the dept. of community genetics, who is either a physician, a clinical geneticist, a genetic consultant or a nurse will inform the family and to a functionary in the hospital (see 11.2), The authorized functionary will coordinate the referral of the parents to the appropriate medical functionary, according to the result and the preferences of the parents. He will also report to the local public health office in the vicinity of the parents. Should the authorized functionary fails to locate the parents or has difficulties in communication with the parents, the public health office will help find the parents and communicate with them.

11.2 Diagnosis and follow up

11.2.1 The parents will be referred to one of the hospitals participating in the screening program for the sake of diagnosis (establishment or ruling out the screened diagnosis) and initiation of therapy. However, all cases of possible PKU will be referred to the national PKU clinic in Sheba medical center.

12. Affiliation of hospitals with the program for diagnosis and treatment

21.1 In order to join the program, the hospital management should write to the dept. of community genetics and propose a physician expert either in metabolic or in endocrine diseases.

21.2 The hospital manager should take care that the [above] experts be available all year long. In case of absence, the expert will inform the lab about his replacement and how to reach him. The lab will refer patients with abnormal results to these doctors.

12.3 The above mentioned experts should participate in every meeting dedicated to NBS, which will be organized by the dept. of community genetics (up to twice a year).

12.4 The dept. of community genetics will reimburse the hospital for the care provided to outpatient neonates. The reimbursement will be for visit/consultation of an expert doctor and the costs of initial lab tests whose purpose is either to establish or to rule out the screening's result. The rate will be determined by the ministry of health. Other aspects of care and follow up will be covered by the medical insurance (*Kuppat Holim*).

Appendix D – Transfer of Mother and Newborn from Home Delivery to Hospital

To: Delivery Room, _____ Hospital

Mother's name: _____

Identity No.: _____

OB/GYN history: Normal / Abnormal Specify: _____

Mother's blood type: _____ Rh: _____

Reason for transferring the mother and newborn to the hospital:

Pregnancy monitoring card attached / not attached

Midwife's / Doctor's particulars

Name: _____ License No.: _____

Address: _____

Telephone numbers: _____

Signature and stamp: _____

4. Refusal form, NBS (Appendix to Ministry of Health Ordinance 02/2009)

Hospital / site of birth: _____ Surname: _____

Neonate full I.D. _____ Date of birth _____

Mother's full name: _____ Mother's birth date: _____

By signing this document I affirm the following:

I have received and read the Ministry of Health's brochure "Information to a woman that is going to give birth, including [information] on screening of healthy newborns.

It has been explained to me that the screening tests are recommended by the ministry of health and [that they are] aimed at the detection of severe diseases of the kind that may be prevented or ameliorated by means of early detection and prompt treatment.

I understand that prompt treatment depends on the earliest possible testing, but not before 36-48 hours postnatally.

It has been explained to me, and I understand that some of the diseases targeted by the screening test may be symptomatic even during the first days of life.

It has been explained to me that the purpose of screening all newborns is the facilitation of early diagnosis and preventive treatments that must be instituted before irreversible harm to the newborn occurs, including mental retardation and death from metabolic diseases.

I have received the explanation and I understand the risks to the health of my child owing to my refusal to test him / her.

After a conversation about the matter with _____ and regarding all of the above points, I refuse the testing of my child.

Signatures:

Mother _____ full name _____ I. D. _____

Father: _____ full name _____ I.D. _____

[Healthcare professional] providing the information: _____

His / her specialty _____

Comments:

The birthing mother or the legal guardian (adoption / surrogacy / minor woman) must sign the document. It is preferable to make the father sign as well. The informers should be the head of neonatal services or a person s/he has nominated for this purpose. The signed document should be filed in the patients [=baby's] medical records. A bloodless [Guthrie] card should be sent to the lab with the personal information and the note that the mother/parents has refused NBS.

5. Israel Genetic Information Act (2000)

The English translation of the law is 21 pages long. Here is a link to a pdf document:

<http://www.jewishvirtuallibrary.org/jsource/Health/GeneticInformationLaw.pdf>

The most updated version of the proposal to amend this law is found (in Hebrew) in the official website of the Israeli Parliament.

www.knesset.gov.il/privatelaw/data/19/399.rtf

6. *“Jewish” Genetic Diseases*

This is not a strictly scientific title. However, some genetic conditions are considered relatively common among the Jews. Even though the Jewish people has a unified ethnic identity, physical and genetic traits are divided into two prototypical groups: “Ashkenazi” (= those of European descent) and “Sephardic” (= those of oriental descent). The list below is taken from the website of the non-for profit “Jewish Genetic Disease Consortium”.

Ashkenazi Jewish Genetic Diseases

Bloom’s Syndrome (BS)
Canavan Disease
Cystic Fibrosis (CF)
Familial Dysautonomia (FD)
Familial Hyperinsulinism
Fanconi Anemia Type C
Gaucher Disease Type 1
Glycogen Storage Disorder Type 1A (GSD 1A)
Joubert Syndrome Type 2
Lipoamide Dehydrogenase Deficiency (E3)
Maple Syrup Urine Disease (MSUD)
Mucopolysaccharidosis Type 4 (MPS4)
Nemaline Myopathy
Niemann-Pick Disease Type A
Spinal Muscular Atrophy (SMA)
Tay-Sachs Disease
Usher Syndrome Type 3
Usher Syndrome Type I
Walker Warburg Syndrome (WWS)

Sephardic/Mizrahi Jewish Genetic Diseases

Alpha-Thalassemia
Ataxia Telangiectasia
Beta-Thalassemia
Corticosterone Methyltransferase Type II Deficiency
Costeff Optical Atrophy
Cystic Fibrosis (CF)
Familial Creutzfeldt-Jakob Disease
Familial Mediterranean Fever
Familial Tumoral Calcinosis (Normophosphatemic Type)
Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD)
Inclusion Body Myopathy 2
Limb Girdle Muscular Dystrophy Type 2B
Metachromatic Leukodystrophy (MLD)
Polyglandular Deficiency Syndrome
Pseudocholinesterase Deficiency
Spinal Muscular Atrophy (SMA)
Wolman Disease

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