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Stakeholder views about participating in paediatric biobanks: a narrative review

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Abstract

Scientific and medical research with children is essential to the development of therapies for younger patients. Paediatric biobanking uses samples from minors to provide a critical and expanding resource for such research. It also raises important ethical, legal and social implications (ELSI) and highlights the need for appropriate frameworks for practice developed through stakeholder consultation. This paper reviews the current literature on stakeholder views of paediatric biobanking. A narrative review was conducted of empirical studies in this area, the majority of which did not involve actual biobanks or include the views of children. Key themes were identified: parental consent; childrens' assent; the return of results; and risks, benefits and burdens of participation. The resultant analysis highlights how children involved in paediatric biobanks are not only capable of understanding and assenting to their participation but also of contributing their voices to the development of future paediatric biobanking policy.

Key words: paediatric biobank, children, ethics, narrative review, genetic, social

1. Introduction

The use of human samples in biomedical research has resulted in unprecedented scientific breakthroughs (Wolf, Bouley et al. 2010). Biobanking technology today offers a rich resource for studying many aspects of human health and disease. The Organisation for Economic Co-operation and Development defines biobanks as “a collection of biological material and the associated data and information stored in an organised system, for a population or a large subset of a population” (Sampogna 2006). Paediatric biobanking promises greater understanding of the causes, prevention and treatment of childhood disease (Brisson, Matsui et al. 2012). The ongoing dearth of knowledge of preventive measures and appropriate treatment for children at different stages of their development is internationally recognised (Gill 2004). This limitation results in part from stringent child protection restrictions placed on research involving children (Avard, Silverstein et al. 2009). But alongside the need for child protection in research is an equal and growing need for the inclusion of child participants in order to generate age-specific findings (Field and Behrman 2004). Paediatric biobanks continue to be developed as a basis for facilitating medical and scientific research with samples from child populations (Samuël, Knoppers et al. 2012). Their development has been accompanied by a corresponding interest in the ethics of children’s participation in research and a need for sociological inquiry into practices connected to it (Avard, Sénécal et al. 2011). Future understandings can be

expected to aid in policy development and the implementation of culturally appropriate paediatric biobanking practices.

Paediatric biobanking is governed by myriad restrictions and regulations, an unsurprising situation given the historical injustices in bioscience perpetrated on vulnerable populations (Avard, Silverstein et al. 2009) and the controversial discovery of unconsented bio-repositories such as those at Alder Hey hospital and Bristol Royal Infirmary in the UK (Boden, Epstein et al. 2009, Avard, Sénécal et al. 2011). There is also ongoing limited guidance on promoting good biobanking practices involving samples from children (Samuël, Knoppers et al. 2012). In paediatric biobanking, participants are in a state of growing maturity requiring researchers to address issues of privacy, autonomy and concepts of risk that all change with age. Some argue that research on children should only be undertaken if it involves no more than minimal risks, namely those no higher than what a child would encounter in daily life (Hens, Nys et al. 2009). A dynamic approach to paediatric biobanking has also been put forward (Avard, Silverstein et al. 2009), one founded on continued communication among all stakeholders (for example, the model proposed by (Kaye, Whitley et al. 2014)).

Children are key stakeholders and have demonstrable knowledge of the benefits and challenges of biobank participation (Anderson, Stackhouse et al. 2011). Considering their views in research recognizes their worth as human beings (Roberts 2008) and potentially improves the protection of children while fostering trust in biobanking (Lemke, Wolf et al. 2010). Such

consultation may also help highlight pitfalls in research design and provide opportunities for improving research (Godard, Marshall et al. 2004). The *UN Convention on the Rights of the Child* states that children capable of forming their own views should be assured their right to express these views on matters concerning them (Morrow and Richards 1996). The *Children's Act of 1989* in England and Wales stipulates that courts shall regard the wishes and feelings of the child, while professional bodies such as the British Psychological Association and the British Sociological Association as well as research organisations such as the Medical Research Council encourage active consultation and engagement with children involved in research.

Little is known, however, about children's understandings of their social positioning within health research (Mayall 1998). Children are increasingly seen as competent social actors worthy of study in their own right (James and James 2001), and that understanding childhood requires revealing the experiences of children (Shanahan 2007). But giving voice to children entails more than simply letting children speak; it necessitates a deeper exploration of their experiences and how adults theorise these (James 2007). Understanding social order from a child's standpoint requires studying not only a child's perceptions but also the development of the concepts that underpin such knowledge (Mayall 1998). Social studies of paediatric biobanking is therefore needed to inform more fully policies affecting the study of health and disease in children (Grover 2004).

While paediatric research must always be finely balanced against child protection (Mumford 1999), overweighting in favor of protectionism can result in ‘therapeutic orphans’ and a limited number therapies tested for safety and efficacy in children (Samuël, Ries et al. 2008). The construction of children’s vulnerability may also lead some researchers to view child participants as ‘out-of-bounds’ with the result that their voices are silenced (Moran-Ellis 2010). Past efforts to advance research while maintaining effective child protection have rested on the principle of subsidiarity; that is, permitting research on children only if it cannot be done on adults (Hens, Van El et al. 2012). Research with children has also generally been based on the precautionary principle that adequate measures must be taken to avoid potentially harmful outcomes when there is an expectation based on empirical evidence or causal hypotheses that damage could occur (Jarosinska and Gee 2007). This approach demands full consideration be given to any physical and emotional harm to the child, such as avoiding venipuncture by using residual blood from diagnostic testing, or conducting data collection at home or a familiar setting rather than in a hospital (Avard, Silverstein et al. 2009). Risks specifically associated with biobank participation include breaches of privacy, the disclosure of information to third parties, and possible stigmatisation of participants based on genetic results (Avard, Silverstein et al. 2009).

The objective of this paper is, therefore, to identify and critically review existing empirical research into the views and perspectives of principal stakeholders involved in paediatric biobanking – namely children, parents

and researchers. The authors aim to summarise not only key findings emerging from this literature, but also to critically examine higher level ethical, legal and social implications (ELSI) issues cross cutting the existing evidence base. The authors assume from the outset that children's voices are essential to future development of paediatric biobanking policies and best practice.

2. Methods

A narrative approach was used to review the literature. The aim was to identify empirical research involving stakeholders and/or participants in paediatric biobanks. A narrative rather than systematic review was undertaken for reasons outlined in the literature (Petticrew and Roberts 2008, Bryman 2012), namely: that the focus of the review was broad rather than specific; the studies under consideration were largely qualitative or mixed methods; and the objective was to assess individual studies rather conduct a meta-analysis. A literature search was conducted by the lead author (CO) to identify all articles published in English prior to May 2014 using multiple bibliographic databases. The search process was iterative and continued until no new articles were found (Petticrew and Roberts 2008). The overall strategy was additionally reviewed for quality and output by a second author (JM), who is a professional librarian.

In order to pinpoint search terms most applicable in the field of paediatric biobanking, an initial pilot search was conducted using the Web of Knowledge (WoK) bibliographic database. An analysis of the results from

exploratory searching determined that virtually all relevant papers included keywords on two themes: children and genetic databases. There was, however, considerable variation in terminology use. The terms relating to children were *child/children*, *minor*, *youth*, *young people*, *adolescent* and *paediatric*; while those relating to genetic databases were *biobank(s)*, *gene bank(s)*, *gene repository/ies*, *genetic database(s)*, *stored DNA* and *genomic database(s)*. Based on these pilot efforts, an initial search was conducted in WoK using the terms identified above for children and genetic databases. The final search used was:

TOPIC: (child* OR minor OR youth OR young people OR adolescent OR paediatric) AND

TOPIC: (biobank* OR gene bank* OR gene repositor* OR genetic database* OR stored DNA OR genetic repository* OR genomic database*)

The search (along with all subsequent updating searches) was conducted without date restrictions because paediatric biobanking remains a relatively new practice whose documented evidence base is small. Initially we focused on general population biobanks that either included mainly or only children. As these efforts yielded few papers, it was decided that disease-specific tissue banks should also be included to elicit a range of views about children's participation in biobanking more broadly.

The final WoK search (May 2014) produced 311 unique hits. These were assessed by reviewing each paper's keywords and abstract using predefined inclusion and exclusion criteria. Papers were included for

review if they reported findings from empirical studies into people's opinions, views, perceptions or experiences with a paediatric biobank, paediatric tissue bank, or any biobank and tissue bank including or intended to include samples from children. Papers excluded from review were those of a medical laboratory nature, those detailing the structures of biobanks, any papers based on blood spots or Guthrie cards, those focusing on predictive genetic screening, and publications not based on empirical studies (e.g. theoretical papers, systematic reviews, legal document reviews). Papers were also excluded from review if they were not published in English or if full-text versions could not be obtained. Some papers included for review sought participants' views on the idea of paediatric biobanking rather than actual paediatric biobanks. For the purposes of this paper these were categorised as being "hypothetical" biobanks owing to the fact that the biobanks either did not exist or were being established but not yet operational.

The WoK search was then repeated in PubMed (119 hits) and Scopus (195 hits). A total of 11 articles met the inclusion criteria. Following all three searches, a similar and final search was conducted using Google Scholar (GS). Because GS offers a less precise search interface, the search strategy incorporated additional terms relating to research methods and study type. Of the terms used, the first was 'paediatric biobank', the second focused on research methodology (e.g. qualitative, empirical, thoughts, views, experiences) and the third related to study type (e.g. birth cohort, longitudinal). Within GS the final search used was:

paediatric biobank AND qualitative OR empirical OR thoughts OR views OR experiences AND longitudinal birth cohort

Two further articles were identified using GS. To ensure a comprehensive literature review, a 'pearl growing' (Bryman 2012) assessment of the references cited in all 13 articles was carried out. This produced two further articles that met the inclusion criteria, for a total of 15.

When conducting a narrative review, Bryman (Bryman 2012) also recommends reviewing key authors' publications. Based on papers assessed for inclusion, several researchers were identified as prominent in the broader field of paediatric biobanking through their involvement in either empirical or theoretical research. A search for each was conducted in WoK and PubMed, identifying one further paper. Corresponding authors of all 16 papers were contacted by CO to inquire if further work had been completed or published. This yielded six papers for a total of 22. Emails were also sent to 70 paediatric biobanks and biobanks involving families requesting references, though no new articles meeting the inclusion criteria were identified.

3. Results

The results section first provides a brief overview of the papers and the different types of research undertaken. Secondly we identify four main themes emerging from the findings and considers their implication for future research and practice in paediatric biobanking.

3.1. Summary of papers reviewed

All papers reviewed are summarised in Table 1. Four key characteristics were identified among them. First, the 22 papers reported only 17 empirical studies (papers reporting on single underlying studies were: Study A (Halverson and Ross 2012, Lemke, Halverson et al. 2012); Study B (Goodenough, Williamson et al. 2003, Goodenough, Williamson et al. 2004, Williamson, Goodenough et al. 2004); and Study C (Hens and Dierickx 2010, Hens, Nys et al. 2010). Second, only one study sought solely children's views about their experience of participating in biobank research (Goodenough, Williamson et al. 2003, Goodenough, Williamson et al. 2004). Two others (Dixon-Woods, Wilson et al. 2008, Harris, Ziniel et al. 2012) included both children and adults, though these were based on tissue bank research (i.e. disease specific biobanks); in these papers the contribution of children was not made explicit in the findings. One study included adolescents (i.e. children in their teens) as well as adults (Hens and Dierickx 2010, Hens, Nys et al. 2010). Third, a clear majority of the papers (n=13) involved what we have termed hypothetical paediatric biobanks (i.e. biobanks that did not exist at the time of the study). Finally, almost all authors referred to children, minors or adolescents without specifying age ranges (for this paper, we use *child* or *children* to refer to any individual under 18 unless specified otherwise by an author).

3.2. **Themes arising from the review**

Four main themes emerged from the literature reviewed on paediatric biobanks. These were: (1) parental consent; (2) children's assent; (3) return of genetic results; and (4) risks, burdens and benefits of

participation. Each is discussed in turn, after which we briefly compare the perspectives of the range of stakeholders involved in the reviewed studies.

3.2.1. **Parental consent**

Parental consent was a recurrent theme in many of the papers. Although never defined explicitly, parental consent was understood as parents' agreement that samples, medical records and other information about their children would come to be included in biobanks as well as agreement to their child's ongoing participation. Consent was portrayed as a legally binding agreement given by a parent or a child who had reached the age of majority (usually age 16 years). Overall there was a general preference for involvement in biobanks that used broad consent and simple consent forms (Lemke, Halverson et al. 2012). While seeking views of women about a hypothetical paediatric biobank Neidich et. al. (2008) found that women supported the use of samples for a wide array of paediatric conditions, either to help their own children or medical science more generally. There was some variability regarding temporal restrictions on broad consent, with some studies suggesting parents preferred re-contact about future research (Lemke, Halverson et al. 2012), while others indicated a more general willingness to sanction future research without being re-contacted (McMurter, Parker et al. 2011).

Contrary to common practice in consent taking, parents reported a preference for more straightforward and uncomplicated consenting procedures particularly in the nature of the consent forms (Hens and

Dierickx 2010). For example, a study proposing a hypothetical biobank (McMurter, Parker et al. 2011) found that parents of paediatric oncology patients would be satisfied to give a simple 'yes/no' consent to future research without the need for complicated consent forms. Another (Hens and Dierickx 2010) found researchers and healthcare professionals in genetic research believed that parents would have less confidence in research and be less likely to participate in paediatric biobanks if presented with long consent forms, suggesting more complex consent forms could possibly deter participation among parents.

Parental consent on behalf of children was seen as potentially problematic. Professionals in the field of genetics felt that proxy consent (consent given by parents on behalf of children) could infringe on the child's rights by limiting the scope of the child's assent (Hens, Snoeck et al. 2010). Williamson et. al. (2004) postulated that power is negotiated between parents and children in a complex manner and that the position of children changes as they age and acquire more information.

3.2.2. **Children's assent**

Children's assent was seen as the inclusion of a child's permission – or more simply, a child's agreement – to participate in research, once parental consent had been given on behalf of the child. All papers reported that children's views needed to be taken into account as part of paediatric biobanking practices. In particular, this theme identified a debate over how assent was managed empirically. The issues identified included: when to presume consent (age versus maturity) (Hens and

Dierickx 2010); how to assent (Jackson, Dixon-Woods et al. 2009); whether to re-contact children to update consent (Goldenberg, Hull et al. 2009); and whether to make provisions for withdrawal from research (Ries, LeGrandeur et al. 2010). In their study involving parents of paediatric oncology patients, McMurter et. al. (2011) found that parents considered children capable of consent before the age of 18. Jackson et. al. (2009) affirmed this finding in their study of healthcare professionals but additionally found that strict formal adherence to assessing a child's capacity (such as requiring his/her signature or having a particular age set for majority) could interfere with the assessment of the child's ability to consent. Hens et. al. (2010) corroborated this finding in their study of professionals involved in paediatric biobanking, although their main departure from Jackson was their suggestion that 16 to 18 is a suitable age for children to consent. Jackson et al (2009) argued that specific age boundaries for consenting were too restrictive. Hens et al (2010) did, however, acknowledged the impracticality of assigning a fixed threshold for consent given the influence of an individual child's maturity and social context. Williamson et. al. (2004) reported that child participants viewed consent as a progressive relationship between themselves, their parents and researchers. Hens and Dierickx (2010) postulated that consent forms as used today mainly serve as a document for avoiding prosecution or litigation rather than being a document to improve patient-researcher relationship. Williamson et al. (2004) affirmed in their research with child participants of a biobank that children were cognisant of their changing priorities and opinions and could hence discuss their perceptions of their

own development logically. Additionally, in the case of long-term paediatric biobanking, competence and autonomy were thought to develop through direct social experience (Hens and Dierickx 2010).

Kaufman et. al. (2008) demonstrated that adults saw the importance of obtaining children's permission before inclusion in a biobank. Using a hypothetical scenario approach, Hens and Dierickx (2010) found that teenagers wanted to be re-contacted when participating in research for reasons of respect and curiosity rather desire to control the research. The issue of re-contact for consent was also reported by Goldenberg et. al. (2009), who surveyed adult cancer patients about a hypothetical paediatric biobank that would include a sample from their childhood; in this case re-consent was seen primarily by respondents as indicative of the researchers' respect for participants' interest in research decision making. The debate on re-consent was presented as moving in tandem with a participant's ability to withdraw from a study (2008). While the right to withdraw upheld an individual's autonomy, it also restricted the potential for long term research. One reported way of avoiding high rates of withdrawal was to design participation in biobanks that allowed participants to waive future consent (Goldenberg, Hull et al. 2009). Williamson et. al. (2004) reported that some children felt pressure against dissenting to research participation in their study among child participants of a biobank.

3.2.3. **Return of results to children or families**

Also identified in the analysis was a desire for the return of research results in paediatric biobanking (McMurter, Parker et al. 2011). There was variation in participants' expectations by way of returned results and how these would be communicated. Parents generally wanted some degree of feedback. For example, Harris et. al. (2012) found parents who had enrolled their children (with developmental disorders) in a tissue bank not only wanted to receive results but preferred to receive this information electronically, believing the results would help them understand their child's condition more fully. Additionally, Hens and Dierickx (2010) found that even though participants understood there to be a clear distinction between research and diagnosis, return of results was considered a humane act as compensation for research participation.

Although parents generally wanted results returned, this desire led to secondary concerns, especially tensions between a child's autonomy and privacy vis-a-vis his/her parents (Hens and Dierickx 2010). The study found there was a need to strike a balance between a parent's desire for disclosure and a child's autonomy within research participation. This debate was also addressed by Hens et. al. (2010), who argued that communicating genetic results that lacked immediate medical value to parents would breach the principle of autonomy and affect the child's ability for self-governance. In addition to this, Harris et. al. (2012) postulated that a child's future autonomy in controlling their research results may be compromised when such results are disclosed to his/her legal guardian. Similarly, Hens and Dierickx (2010) argued that the rights of a child to know about (potentially treatable) medical conditions

superseded the rights of his/her guardians in deciding not to know. Likewise, it was reported that returning genetic results could alter how parents treat their child (Hens, Nys et al. 2010). Such debates speak to ongoing concerns about best practices for upholding the autonomy of a child in paediatric biobanking.

3.2.4. **Risks, burdens and benefits of participation**

The final theme addressed the balance between the risks and burdens of research and the potential benefits that could come from participation. While definition of terms such as *risks*, *burdens* and *benefits* was rarely made explicit in the papers, *risks* were mainly viewed as potential harms, *burdens* as excessive demands in time and effort, and *benefits* as possible gains from participation (including but not limited to financial or therapeutic gains). In the papers reviewed, the specific risks faced by children from biobanking were varied, from physical or emotional harm (a commonly reported example was venepuncture, though whether this meets the minimum risk threshold for child research participation may be debatable), to being uncomfortable socially with certain questions (e.g. questions about alcohol consumption among teenagers) (Hens and Dierickx 2010).

A number of authors reported concern among researchers and the public to avoid risks and burdens for research participants. Others reported a similar finding among parents and children. Halverson and Ross (2012) specifically noted parents stating they would enrol their children in a biobank on condition of minimal risk to the children. Kaufman et. al.

(2008) found parents in their study were not willing to enrol their children in biobanks because participation would be burdensome, especially if the biobank required daily recording of a child's life, vis a vis the already long list of activities of their children. Hens et. al. (2010) reported that the possibility of research being distressing or of limited benefit to participants could inhibit enrolment in biobanks. Public opinion, as presented by Kaufman et. al. (2008), revealed an expectation of benefits to individuals such as the child or the child's family, or a wider benefit to society through the advancement of medical knowledge. In spite of participants being concerned by the level of burden placed on them by participation, Lemke et. al. (2012) also found that parents believed the benefits of participating in a paediatric biobank outweighed the risks. Although parents wished to protect their children from unwarranted burden and risks, they were aware that certain risks are ubiquitous in society; and reasoned that no research is exempt from risk in the form of breaches (Lemke, Halverson et al. 2012).

4. Multiple stakeholders

A range of stakeholder opinions were covered in the papers included in this review. We note the specific patterns of these perspectives here. In papers reporting researchers' opinions, the issues resonating most were the need for both parental consent and child's assent (Jackson, Dixon-Woods et al. 2009, Hens and Dierickx 2010), the problematic nature of both blanket consent (Ries, LeGrandeur et al. 2010) and the return of research results (Ries, LeGrandeur et al. 2010), the need for privacy

protection, and a concern that research should not be burdensome to the child (Hens, Snoeck et al. 2010). Papers reporting views of parents demonstrated that there was a general desire to receive research results (McMurter, Parker et al. 2011, Harris, Ziniel et al. 2012, Lemke, Halverson et al. 2012) and that children should be re-contacted as they matured (McMurter, Parker et al. 2011) for consent (Klima, Fitzgerald-Butt et al. 2013). Parents supported biobank use for a wide array of paediatric research (Neidich, Joseph et al. 2008) and their enrolment was based on their trust in biobanks (Neidich, Joseph et al. 2008, Brothers and Clayton 2012). Parents asserted that children should be given access to their health records (Halverson and Ross 2012). Papers reporting the views of the public had similar themes: the need for re-consenting after the child reaches majority (Kaufman, Geller et al. 2008, Goldenberg, Hull et al. 2009), the need for minimising a child's pain and burden in participation (Kaufman, Geller et al. 2008), a desire to receive research results (Halverson and Ross 2012), and the importance of trust in research participation (Halverson and Ross 2012). Papers involving both adolescents and adults (who were not participants in biobanks) reported similar findings, (though it is not clear which responses were from the adults and which ones were from the adolescents): that research should not be burdensome (Hens and Dierickx 2010); a trust in parents ability to consent to the right research as well as trust in biobanking (Hens, Nys et al. 2010); the importance of informed consent and growth toward autonomy (Hens and Dierickx 2010, Hens, Nys et al. 2010); the need for confidentiality; and, wanting meaningful research results communicated

(Hens, Nys et al. 2010). Papers reporting the views of children alone or children and parents (actual biobank participants) expressed the need for both child's assent and parental consent (Goodenough, Williamson et al. 2004, Williamson, Goodenough et al. 2004) the need for anonymity (Goodenough, Williamson et al. 2004) and the growing autonomy of children (Goodenough, Williamson et al. 2004).

Discussion

This review highlighted four main areas of interest in paediatric biobanking. First, parents preferred simple consenting procedures, though it was noted that broad parental consent can be problematic if it impairs a child's future autonomy and control over their participation in research. Second, children's assent was considered important in research. The few children interviewed in these empirical studies viewed their role in assent as a progressive relationship between themselves, their parents, the researchers. Child participants expected that with increasing age they would have more control over their research participation. There was, however, varied opinion as to the correct age for children to assume consenting responsibilities for research. Many child respondents held the view that children might find it difficult to exercise their right to dissent to research consented by their parents. Third, the return of research results is a particularly important issue. Parents generally wanted to receive results, viewing them as a possible benefit of participation in a biobank. Some authors however understood this activity as having the capacity to infringe upon a child's autonomy. Finally, concern about risks, burdens and

benefits of research participation was evident in the literature. Respondents in all studies wanted research to involve minimal risks and to not be burdensome. Parents supported biobank participation on condition that the associated benefits outweighed the risks.

That consent and assent continue to be debated in paediatric research literature is unsurprising. While assent as defined by Alderson (2007) comprises a non-refusal or simple agreement without the understanding, discretion and legal validity associated with consent, consent invokes protection of one's integrity of body, mind and personal information (Miller and Boulton 2007). The latter is a concept with a dual ethical and legal nature (Brothers 2011). The consenting process in a paediatric research setting is ideally fashioned as a tripartite relationship between parents, children and researchers, though more probably involves value judgments by the parent or child's guardian rather than risk assessment or acceptance by the child. This is especially true where children are very young (e.g. in a birth cohort study) and parents give proxy consent based on a substituted judgment (i.e. the presumed judgment of child if he or she was competent) (Samuël, Knoppers et al. 2012). There is, of course, no guarantee that the guardian's decision is the same as the child's will. As children age it is necessary to examine their views on the consenting process to unlock pragmatic and ethical ways of handling this necessarily dynamic and changing relationship. Indeed, there are numerous examples in the field of paediatric biobanking of potentially good practice, though these are not often documented or verified by or with child participants themselves.

Understandable concerns about the potential risks of research participation in this literature raise issues about definitions and perceptions of risk. Framing potential dis-benefits of research as risks may be itself problematic: absence of risk is not commensurate with the absence of cost (Williams 2012). There may, for example, be relational or power impacts or costs. In as much as dissent is available for children – they are able to interpret social behaviour and develop social expectations of themselves (Davis 1998) – such dissent may be difficult in practical and emotional terms. A child's dissent may be treated as non-cooperation; and could bear a cost in the relational dynamic within the tripartite relationship, a relationship involving important power negotiations. Arguably, inequalities of power will always exist for children involved in research (Harden, Scott et al. 2000). While children are active social agents, their lives are in many ways determined for them (Neale and Smart 1998). The aim of including children in research and in debates about research is to avoid the situation whereby 'children have a voice but adults control the conversation' (Shanahan 2007). Irwin (2006) proposed handling this power imbalance in research through the use of an emancipatory model; one having the capacity to increase the children's influence over research without necessarily suggesting that the children should take over the research as is the case with participatory action research (Alderson 2007). Emancipatory research within paediatric biobanking addresses issues of power and respect and has the potential to inform its practice by taking into account the children's' perspectives on the research.

The return of research results is keenly debated in the broader literature about biobanking. Guidelines for return of results routinely recommend that results should only be returned if they have analytic validity, clinical validity, and action-ability, and that the results themselves meet criteria related to severity of outcome (Hens, Van El et al. 2012, Knoppers, Zawati et al. 2012, Wolf, Crock et al. 2012). The return of results is sometimes viewed as a way of benefit sharing in research and by extension is an incentive for participation (Tabor, Brazg et al. 2011). In the papers reviewed here, parents in tissue banks expressed a belief that research participation lead to the development of new medications that could benefit them and their children. This perspective may propagate the expectation and misconception of therapeutic gain from research with a primarily scientific and non-therapeutic aim (Halverson and Ross 2012). In population biobanks, the equivalent misconception may be of the potential diagnostic benefits of research participation (Clayton and Ross 2006). Brothers (2011) argues that biobanks, especially those with de-identifiable resources, are not designed with the aim of, or capacity for, returning health-related results; also referred to as incidental findings.

The studies in this review presented parental and adult perspectives that positioned children as lacking (if only in part) the capacity to make decisions about themselves and how they interact in the world. Historically, children have been viewed in contrast to adults, typically framed as victims or deviants when their views or performance differ from those of adults (Hood, Kelley et al. 1996). Paediatric research has been known to ascribe incompetence to children in a similar fashion, with the

result that it is typically easier to prove a child's incompetence than it is for them to display their competence. And yet by the age of 5 years, a child has already developed a lifelong understanding of self, others, relationships and time (Alderson 2007, Uprichard 2008). Alderson (2007) argues children not only value interpersonal relationships, but they also have the ability to act responsibly and maintain these relationships. Children display sensitivity about differences in age and are generally eager to grow older due to their anticipation of a change in status (Bühler-Niederberger 2010). Ageing throughout childhood involves a relationship between body, self and society (Uprichard 2008). The creation and reproduction of youth sub-cultures selectively adopt and reject adult rules and interpretations (Shanahan 2007). Children appropriate information from the adult world and use it to constitute their own realities (Shanahan 2007). Although children borrow their parents' constructions (e.g. risk), they ultimately negotiate their own understandings (Hood, Kelley et al. 1996). Swartling et. al. (2011) have argued that the development of appropriate frameworks for research with children will only occur when adequate opportunities are available for adults to consult with children and consider as valid children's experiences and views. On this basis, the current literature on participant experience in paediatric biobanking is very much still in its infancy.

5. **Conclusion**

In as much as the papers under review identified key themes in the views of stakeholders' participating in paediatric biobanks, very little of the evidence came from or could clearly be identified as coming from

children. Moreover, much of the literature involving children and scientific and medical research is more generally contextualised within ethical debates (Harden, Scott et al. 2000) and assumes a largely protectionist perspective (Shanahan 2007). This social construction of children's vulnerability gives rise to the perception that children as research subjects are 'out-of-bounds', with the result that their voices are silenced (Moran-Ellis 2010). This situations propagates a dependency model and undermines the status of children as individuals in their own rights (Shanahan 2007). While there remains a need to balance inclusion of children in research with their protection (Avard, Silverstein et al. 2009), it is important to consider how efforts made to protect children may unintentionally protect the power of adults. But the role of children in research is evolving and the shift from their being silent and obedient subjects to autonomous and articulate participants (Alderson 2007) means appropriate biobanking practices involving children will occur as this stakeholder group is actively consulted (Goodenough, Williamson et al. 2004). Children have sophisticated understanding of concepts and issues surrounding genetics (Anderson, Stackhouse et al. 2011) and can contribute to complex policy debates on the topic (Grover 2004). Their virtual absence from empirical research at present is a critical omission to future development of paediatric biobanking policy.

Limitations of the study

This paper examined stakeholders' perceptions of paediatric biobanks by aggregating studies of general population biobanks involving mainly or

only children with studies of disease-specific tissue banks of the same age group. Although this aggregation helped overcome the limited evidence base, our analysis was in turn unable to distinguish between possible differences in attitudes among stakeholders in biobanks and those among stakeholders in disease-specific tissues banks. Our findings suggested attitudes between the two groups converge towards similar themes, though this finding could be challenged as more studies emerge. Our analysis was also limited in that the majority of the studies included were based stakeholders' hypothetical ideas rather than direct experience, and by the fact that the research designs of some studies suggested additional unpublished findings which could not be identified.

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1TABLE 1 SUMMARISING PAPERS REVIEWED

Authors	**Type of Biobank** actual vs hypothetical population biobank vs tissue bank **Participants**	**Methodology**	**Country**	**Key Findings**
Brothers and Clayton (2012), (Brothers, Westbrook et al. 2013)	Hypothetical, Population biobank Parents (n=65)	Interviews	USA	Parents supported an opt-out model biobank in children and would allow their own child's sample to be included.
Brothers, Westbrook et al. (2013)	Actual , Population biobank Parents (n=237)	Interviews	USA	32.9% of participants were familiar with opt-out biorepository, while 92.4% approve of it based on a brief description.
Dixon-Woods, Wilson et al. (2008)	Actual, Tissue bank Children and parents (n=72)	Interviews	UK	Participants considered themselves to be members of a trusted community where values and interests were shared.
Goldenberg, Hull et al. (2009)	Hypothetical, Tissue bank Adults (n=1186)	Survey (telephone)	USA	67% would not be concerned about the use of childhood samples upon reaching adulthood. Concerned respondents were more likely to be more private about their medical records, less trusting of medical researchers, or African-American.
Goodenough, Williamson et al. (2003)	Actual, Population biobank Children (n=23)	Focus groups	UK	Children aged 8-10 years had valuable contributions to offer on their perceptions of participation in non-therapeutic longitudinal research.
Goodenough, Williamson et al. (2004)	Actual, Population biobank Children (n=40)	Interviews + focus groups	UK	Children have concerns over activities they are asked to take part in as research participants. Research participation fostered a feeling of 'being special' among children.
Halverson and Ross (2012), (Halverson and Ross 2012)	Hypothetical, Population biobank Parents (n=45)	Deliberative engagement + survey	USA	There was strong interest in receiving results, which was a main motivator for participation. The trust they had on the research would determine their enrolment.
Halverson and Ross (2012), (Halverson and Ross 2012)	Hypothetical, Population biobank Parents (n=45)	Deliberative engagement + survey	USA	Most participants stated they would enrol themselves and their children in a biobank. Some opposed enrolling children, particularly children unable to consent.

Harris, Ziniel et al. (2012)	Actual, Tissue bank Parents (n=19)	Focus groups	USA	Parents hoped to receive research results that would help them better understand their children's conditions or contribute to scientific knowledge.
Hens and Dierickx (2010), (Hens, Nys et al. 2010)	Hypothetical, Population biobank Teenagers and adults (n=76)	Focus groups	Belgium	There was a willingness to contribute tissue to research. Participants thought there was need for confidentiality protections. People expected to receive results that could be relevant to them.
Hens and Dierickx (2010)	Hypothetical, Population biobank Researchers (n=10)	Interviews	Belgium, UK, Saudi-Arabia	Long consent forms weren't preferred. Proper privacy and data protection was a need. Good communication considered important. Research on children needed to be for pediatric conditions.
(Hens and Dierickx 2010), Hens, Nys et al. (2010)	Hypothetical, Population Biobank Teenagers and adults (n=76)	Focus groups	Belgium	Research had to benefit and not burden children. Parents needed to engage their children in the decision-making. There was a need for re-contact upon maturity.
Hens, Snoeck et al. (2010)	Hypothetical, Population biobank Researchers (n=64)	Survey (Questionnaire)	Belgium	76.5% thought children should assent when they can comprehend; 51% estimated this to be aged16-18 years.
Jackson, DIXON-WOODS et al. (2009)	Hypothetical, Tissue bank Researchers (n=331)	Survey (Questionnaires)	UK	100% were in favour of using tissue samples from children with cancer for research. 90% said both parent and child should consent. 94% supported 'generic' rather than 'specific' consent.
Kaufman, Geller et al. (2008)	Hypothetical, Population biobank Adults (n=141)	Focus groups	USA	Respondents were concerned with: minimizing children's fear, pain, and burdens; whether to include young children; and how to obtain children's assent.
Klima, Fitzgerald-Butt et al. (2013)	Actual, Tissue bank Children (n=378)	Survey (Consent assessment form)	USA	Parents understood consent for participation, purpose of study, and lack of direct benefit. Conversely, they least understood the indefinite storage of DNA, possible risks of participation, and that study was not for therapy.
Lemke, Halverson et al. (2012)	Hypothetical, Population biobank Parents (n=45)	Deliberative engagement + survey	USA	Focus group themes were: interest in biobank participation, broad consent and re-contact; trust in biobanking; and receiving research results. Survey data indicated same degree of interest in receiving results about themselves and their children.
McMurter, Parker et al. (2011)	Hypothetical, Tissue banking Parents (n=100)	Survey (Questionnaire)	Canada	89% agreed to have tissue sent anywhere for paediatric aims. 76% would permit genetic research even if no impact was anticipated. 41% would not allow painful, research procedures, while 15% would allow regardless of the child's dissent.

Neidich, Joseph et al. (2008)	Hypothetical. Population biobank Parents (n=239)	Survey (oral)	USA	Caucasians were the most willing to enroll their children into a pediatric biobank. Most respondents expressed optimism the results would yield significant benefits that would be distributed fairly.
Papaz, Safi et al. (2012)	Actual, Tissue bank Children and adults (n=3278)	Consent forms	Canada	Leading causes for refusal of consent were lack of interest in research 43%, feeling overwhelmed clinically 14%, and discomfort with genetics 11%.
Ries, LeGrandeur et al. (2010)	Actual, Population biobank Researchers (n=14)	Interviews	Canada, Denmark, England, France, Netherlands, USA	None adopted blanket consent for future use of samples/data. Ethics review of new studies a common requirement. Studies following children past early childhood sought assent/consent as the child matured.
Williamson, Goodenough et al. (2004)	Actual, Paediatric biobank Children (n=167)	Interviews + focus groups	UK	Children's views are important in research and yet they underestimate the amount of control they have in it. Questioned parental rights to long-term use of children's samples.

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