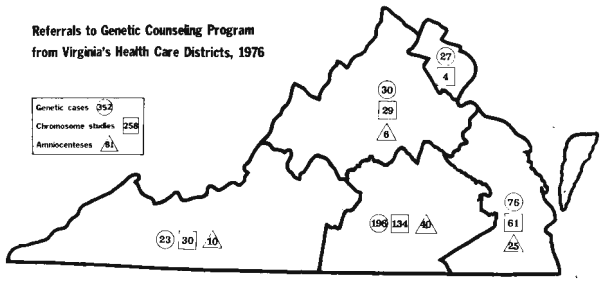
Summary of Genetic Clinic Population: 1973–1977

Classification	Year 1973–75	1976	1977 Jan-June	Total Number	Percent of total
Dominant traits	16	55	40	111	12.2
Recessive traits	46	54	61	161	17.8
Sex-linked traits	16	11	7	34	3.7
Chromosomal disorders	106	258	49	413	45.6
Multifactorial traits	16	24	10	50	5.5
Other conditions	41	55	42	138	15.2
TOTAL	241	457	209	907	100.0

sample included patients with D and E trisomy, the cri du chat syndrome, Turner syndrome, Klinefelter syndrome, the 4p-syndrome, and a variety of structural rearrangements.

Patients classified as having multifactorial diseases included individuals with midline neurologic defects, diabetes, uncomplicated cleft lips and/or palate, clubfeet, seizures, and certain patients with familial mental retardation that could not be otherwise classified. Patients falling into the other categories included individuals with multiple malformations or repeated abortions with normal chromosomes and no other definite causes, or patients with psychomotor retardation of unknown or environmental etiology.

During the year 1976 (Figure), patients came from all parts of the state either to the Genetic Counseling and Amniocentesis Clinics or for diagnostic karyotypic analysis. This pattern of referrals is largely a result of the central location of the Clinic in a large urban area.



Figure—Pattern of referrals to Genetic Counseling Program from Virginia's health care district, 1976.

Population Screening for Genetic Disease

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Recent advances in genetics and laboratory techniques have raised difficult issues for both the medical and lay communities. The desirability of initiating population screening programs is an example of one such issue that has engendered considerable confusion concerning its intent—so much so that the National Academy of Sciences recently reviewed this subject and in 1975 published a book entitled, *Genetic Screening—Programs, Principles and Research.*[1]

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This presentation will describe the four major forms of population screening for genetic disease and, from the Virginia experience with some of them, demonstrate their strengths and shortcomings.

Most readers are already aware of programs to screen for disorders such as hypertension, diabetes, cervical cancer, glaucoma, and other diseases. These programs were established with the idea that they are inexpensive, can be detected by a simple test, and that effective treatment is available. The same principles apply to the four major types of population screening programs for genetic disorders.

1. Carrier detection. Almost all persons are believed to carry approximately four lethal or deleterious recessive genes; however, their existence is usually never known unless the spouse has the same gene, in which case there is a one-in-four chance that each child will inherit a "double dose" of the abnormal gene and develop the disorder. Fortunately, most serious recessive diseases are rare, but there are two—sickle cell disease and Tay-Sachs disease—which are especially prevalent in specific subpopulations and for which simple, reliable, and relatively inexpensive carrier tests are available. Screening programs for detection of heterozygotes (carriers) in both disorders have existed in Virginia for at least five years. Elsewhere in this issue experience with the Medical College of Virginia Sickle Cell Program is described.

Tay-Sachs disease affects approximately 1:4,000 Ashkenazi Jewish births and is invariably lethal by the fourth year because of the abnormal accumulation of a sphingolipid, ganglioside GM_2, in the central nervous system.[2] Hexosaminidase A, the enzyme which is necessary for the normal degradation of this material, is inactive in these patients and is present in only approximately 50% of normal activity in the serum, white blood cells, and other tissues of carriers. Women who are at risk to give birth to such children can therefore be identified *before* pregnancy. If both parents are carriers, an amniocentesis performed in the second trimester can determine the enzyme status of the fetus. If Tay-Sachs disease is found, the parents then have the option to terminate the pregnancy to avert the birth of an affected child.

Measurement of the serum enzyme level is not in itself technically difficult, but so many factors affect its activity (for example, pregnancy, cleanliness of test tubes in which blood is collected, the time during which the serum remains at room temperature before freezing, storage temperature prior to testing, medications taken by patient) that it is not practical for the local physician to forward blood to the testing laboratory from patients wishing their carrier status determined. Although with special precautions and arrangements, testing of remote patients can be done, a more desirable procedure is to schedule periodic mass community testing at various sites. These mobile screening clinics not only obviate the above-mentioned difficulties but they offer a better opportunity to ensure that tested individuals have been properly informed regarding the purpose and possible consequence of the testing. Because this concept of carrier testing is a new one, the most difficult aspect of such screening is to educate the public in the importance of voluntary participation. Most people will not have heard of the disease, and what is more significant they find it difficult to believe that they have a 1:30 chance of being carriers. A second obstacle to successful screening is the lack of funding for such programs. After initial equipment cost outlay, the cost for the Tay-Sachs test averages \$7.00 ± \$2.00, depending on the volume of tests, per individual. The MCV Tay-Sachs Screening Program, operative since 1972, was fortunate to obtain initial support from the Virginia State Department of Health and local Jewish community organizations so that it has been able to offer the test without a fixed charge to tested persons.

As a result of Virginia screening, over 3,700 Jewish persons have been tested at sites in their own cities of Richmond, Norfolk, Newport News, Roanoke, and Fredericksburg; the metropolitan northern Virginia cities have used testing sites in southern Maryland and Washington, D.C., provided by Johns Hopkins Hospital. Over 100 carriers have been identified and counseled, but surprisingly no carrier couple has thus far been found. A full 25% of all adult Jewish people in these cities have been tested. In almost all of the more populous United States cities where testing has been offered for several years, no more than 5% to 10% have appeared for this voluntary test. Clearly, a significant educational effort is needed on two fronts: to convince governmental agencies of the need for appropriate funding for these programs and to inform the public regarding the concept of disease prevention by carrier detection. Support of these efforts is needed soon, for in the very near future carrier detection tests for other more common recessive diseases, such as cystic fibrosis, promise to be available.

Phenylketonuria (PKU) carrier detection is a second test that we currently provide, using a dis-

criminant function, based on serum amino acid levels, that we have recently developed in our laboratory. In this case, since there is no ethnic group in which the gene has a high incidence, we offer the test to the collateral relatives of all new cases of PKU that come to our attention.

2. Antenatal screening. There is a small but clearly definable group of pregnant women for whom screening is indicated because of their substantially increased risk of bearing a child with a genetic disorder. The Antenatal Testing Program, jointly administered by the Departments of Obstetrics and Gynecology, Human Genetics, and Pediatrics, is discussed elsewhere in this issue.

3. Mass neonatal screening. The prototype in this level of screening is the Guthrie test to detect PKU, an assay performed on a dried blood spot obtained in the first week of life. Virginia State law established the program in 1966 and made it the joint responsibility of the parent and/or the physician to provide that the neonate be screened for this condition. Since that time, four to five children with PKU per year (approximately 1:16,000 births) have been discovered and mental retardation averted by maintaining them on a phenylalanine-restricted diet for the first six to seven years of life. The cost for early screening and treatment is approximately one tenth the cost of special education or institutionalization of late-diagnosed, retarded PKU children.

With the demonstrated success of the PKU screening program, many states and foreign countries have established screening programs for other disorders using the same blood spots. The grafting of these additional programs onto an already-existing one and the availability of a machine to handle the blood-spotted filter paper have minimized their cost. The decision of which additional disorders to screen should relate to the following major factors:

a) frequency of the disorder,
b) severity of the untreated disorder,
c) simplicity and sensitivity of the test, and
d) availability of treatment to ameliorate or prevent the disorder.

Under the above considerations, hypothyroidism (by radioimmunoassay of thyroxine), galactosemia (by bacterial inhibition assay), and several aminoacidopathies including homocystinuria, maple syrup urine disease (MSUD), and histidinemia (all also by bacterial inhibition assay) qualify.[3] Because of its frequency (1:6,000) and ease of treatment, and the severity of the mental retardation that ensues due to delayed diagnosis, hypothyroidism warrants immediate development of screening programs.[4,5] Therefore, a neonatal hypothyroid screening program in Virginia is planned for 1978. It is hoped that additional programs for galactosemia and other aminoacidopathies will also be initiated soon.

The spectrum of metabolic disorders screened can be considerably expanded if the urine of two- to three-week old infants is also tested by various simple chromatographic and high-voltage electrophoretic techniques. Such a program, using specimens collected on filter paper at home by the parent and mailed to the central laboratory performing the blood tests, has already been in effect for several years in Massachusetts[6] and several other states. This procedure also serves as a follow-up test to detect neonates with false-negative blood results for the previously mentioned aminoacidopathies, including PKU.

Except for the PKU program, testing for other disorders in Virginia and most other states is and will be voluntary. An advisory committee of consumers, experts in metabolic disease, geneticists, laboratory personnel, clergy, and ethicists is clearly needed to serve as an advisory body to determine the propriety and mode of administration of these proliferating programs.

4. Urine metabolic screening. While the total incidence of inborn errors of metabolism is probably no greater than 1:5,000, these disorders are more often seen in children with mental retardation, seizures, hepatosplenomegaly, recurrent or persistent acidosis, failure to thrive, or unusual odor to urine or sweat. Where the etiology of any of these conditions is unclear, one of the inborn errors of metabolism must be considered; therefore, a variety of simple tests on a random urine specimen is recommended to screen for over 30 such disorders of amino acid, mucopolysaccharide, and carbohydrate metabolism.[7] At the pediatric metabolic laboratory the following tests are routinely performed weekly on a 20 ml acidified random urine specimen received by mail: a) ferric chloride and dinitrophenylhydrazine tests to detect the alpha-keto acid excesses found in PKU, tyrosinemia, MSUD, and histidinemia; b) silver nitroprusside test for homocystinuria; c) Benedict's tablet for reducing substances; d) gross turbidity test for mucopolysaccharidoses; e) isatin spot test for the iminoaciduria of proline or hydroxyproline excess; f) nitrosonaphthol test for tyrosinosis; and g) high-volt-

age separation of all urinary amino acids to detect any excesses. Although the yield of newly diagnosed inborn errors by this screening program is small, those few cases detected are important because they may lead to a specific diagnosis that permits a prognosis, a recurrence risk for other family members, and counseling about the possibility of treatment or prenatal diagnosis for future pregnancies.

Clearly, genetic screening programs are an important component of the primary care physician's efforts in preventive medicine. Participation in and support of these programs is therefore strongly urged.

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The Virginia Sickle Cell Anemia Awareness Program (VaSCAP): Education, Screening, and Counseling

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In 1968, a program of screening for sickle trait carriers was begun as part of the work of the Hematology Division, Department of Medicine, at the Medical College of Virginia. It was felt that sickle cell anemia was more of a public health problem than was generally recognized, and in addition to instituting screening and education programs, data were collected to document the relative neglect of the problem.

A survey of the City of Richmond was conducted to ascertain the level of awareness among

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