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Genetic Screening

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Current approaches to genetic screening include newborn screening to identify infants who would benefit from early treatment, reproductive genetic screening to assist reproductive decision making, and family history assessment to identify individuals who would benefit from additional prevention measures. Although the traditional goal of screening is to identify early disease or risk in order to implement preventive therapy, genetic screening has always included an atypical element—information relevant to reproductive decisions. New technologies offer increasingly comprehensive identification of genetic conditions and susceptibilities. Tests based on these technologies are generating a different approach to screening that seeks to inform individuals about all of their genetic traits and susceptibilities for purposes that incorporate rapid diagnosis, family planning, and expediting of research, as well as the traditional screening goal of improving prevention. Use of these tests in population screening will increase the challenges already encountered in genetic screening programs, including false-positive and ambiguous test results, overdiagnosis, and incidental findings. Whether this approach is desirable requires further empiric research, but it also requires careful deliberation on the part of all concerned, including genomic researchers, clinicians, public health officials, health care payers, and especially those who will be the recipients of this novel screening approach.

genetic testing; genetics, medical; genomics; heterozygote detection; neonatal screening; prenatal diagnosis

INTRODUCTION

Screening is conventionally described as the evaluation of asymptomatic people in a defined population to detect an unsuspected disease or risk in order to improve health outcome (1). Newborn screening to identify infants who would benefit from early treatment is an example and represents a prominent public health service. Genetic screening is also performed in clinical settings to detect carriers of genetic diseases and for prenatal diagnosis, with a different goal: to assist reproductive decision making. Both types of screening were started with a focus on specific conditions (Table 1) (2–9) but have expanded substantially as a result of technological advances.

New technologies allow multiple genetic risks to be ascertained simultaneously and offer new genetic screening opportunities—for example, the potential to detect genetic susceptibilities to common diseases at a level far exceeding that of conventional family history assessment (10). One example of such testing, single nucleotide polymorphism microarray testing, is now available directly to consumers (11). This type of screening uses an array-based platform (12) to measure multiple gene variants associated with disease risk and can provide information about genetic susceptibilities to many different health risks. Some marketing claims emphasize the health value of single nucleotide polymorphism screening—for example, ''By understanding your genetic predispositions, you can start looking at your health in a new way. You can also learn if certain medications work with your genetic makeup'' (13). Tests of this kind are often referred to as ''genome-scale'' because they analyze genetic variation across the full complement of human genetic material or genome. Numerous genome-scale tests are now available (Table 2) (12, 14, 15), each using different methods to measure multiple genetic differences simultaneously.

The ultimate genome-scale test is whole genome sequencing, which ascertains an individual's complete DNA sequence (15). Costs of whole genome sequencing are rapidly diminishing. The first human genome sequence was the end product of the Human Genome Project, a multinational scientific effort that took almost 15 years to complete and cost about $3 billion. However, costs (in the research setting) are now in the range of $10,000–$50,000 per genome. The ''thousand-dollar genome''—perhaps even a hundred-dollar

genome—is expected soon. Whole exome sequencing is a less expensive, but similar testing approach, in which just the protein-coding regions of the genome are sequenced (Table 2). Some experts predict that as costs fall, whole genome sequencing and related genome-scale tests will usher in an era of ''genomic medicine'' (12, 16).

Population screening is a central component of this vision. In this review, we explore the experience with newborn and reproductive genetic screening. We also consider the insights these screening programs provide as genome-scale tests are contemplated for application in the general population.

NEWBORN SCREENING

Newborn screening is now implemented in all developed countries. In the United States, most states screen for at least 29 conditions (Table 3) (17, 18) within the first few days of life as part of state public health programs that have developed over the last half century. For infants with out-of-range findings, the program includes confirmatory testing and referral for medical follow-up (19, 20).

Historical background

Newborn screening began in the 1960s to address a specific disease, phenylketonuria (Table 1). The concept of screening newborns for phenylketonuria was derived from a 30-year research effort to define its biochemical basis (21), develop a diet therapy (22–24), and create a reliable testing mechanism (25). In this context, newborn screening provided an unprecedented opportunity to prevent cognitive impairment in affected infants by rapid initiation of a phenylalanine-poor, tyrosine-enriched diet.

Several factors converged to promote newborn screening for phenylketonuria (26–28). Advocacy organizations, particularly the National Association for Retarded Children, embraced the potential of diet therapy to prevent the complications of phenylketonuria (26). Political will was spurred by the strong interest of the John F. Kennedy family and presidential administration in the issue (27, 29). The result was an alliance among disability advocates, genetics specialists, and political leaders to establish newborn screening state by state. This effort marked a sharp departure from the earlier association of genetics with the eugenics movement (30), and it provided politicians with an attractive opportunity to advocate for child health.

Newborn screening for phenylketonuria also represented an important new connection between genetics and public health. A distinctive feature of phenylketonuria screening was time urgency: infants with phenylketonuria must be identified within 2–3 weeks of birth to derive the full benefit from diet therapy. Thus, a successful newborn screening program requires both a suitable test, with attention to laboratory quality standards, and effective follow-up to assure that all identified children have rapid access to treatment (19, 20). These requirements led to implementation of newborn screening as a legislatively mandated public health program in most states.

The groundswell of advocacy was sufficient to overcome cautions expressed by many in the medical community that the evidence for benefits from newborn screening was weak (31). These cautions were not unreasonable: one historian has estimated that newborn screening for phenylketonuria was promoted on the basis of experience with diet therapy in fewer than 20 infants with the disease (32). In addition, although phenylketonuria screening is considered highly successful, a full understanding of the implications of screening emerged only over time (29, 33). A randomized trial established that diet therapy needed to be lifelong rather than limited to a period of neurologic development in childhood (34), and a stringent diet is required in pregnancy to prevent serious problems in children of women with phenylketonuria (35). Also foreshadowing the complexity of many subsequent newborn screening tests, phenylketonuria screening led to the identification of infants with ''physiologic hyperphenylalanemia'' who were not at risk of cognitive impairment and could potentially be harmed by the diet (29, 36).

Expansion of newborn screening

Gradual growth in testing panels occurred in the years following initiation of phenylketonuria screening. The next condition to be added in most states was congenital hypothyroidism, a nongenetic condition with a time urgency similar to that of phenylketonuria; early treatment of congenital hypothyroidism prevents growth failure and cognitive impairment (37). Testing panels were further expanded as screening tests became available to detect other conditions, mostly genetic, that required treatment in the newborn period.

Many added conditions involved less time urgency or less benefit than phenylketonuria and congenital hypothyroidism. For example, most states implemented newborn screening for sickle cell disease (Table 1) in the 1980s based on evidence that early treatment with antibiotics reduces the risk of sepsis (38). However, initiation of treatment is recommended within the first 4 months (39) rather than the first 2–3 weeks of life. Similarly, many states adopted screening for cystic fibrosis based on randomized trial data showing improved nutritional outcomes among cystic fibrosis infants identified by newborn screening versus clinically (40). Newborn screening is also estimated to provide a small mortality benefit (41, 42). However, a follow-up study of patients in the randomized trial of newborn screening, now between 8 and 18 years of age, showed no benefit from newborn screening for pulmonary disease or health-related quality of life (43). The evolution toward screening that offered less dramatic benefit was described by one expert as moving from ''public health emergency'' to ''public health service'' (44).

A new testing technology introduced in the 1990s, tandem mass spectrometry, dramatically increased the number of results available for newborn screening. Tandem mass spectrometry enables measurement of numerous metabolites and more than 50 metabolic disorders, some still poorly characterized or lacking definitive treatment (17, 45). In addressing technology of this scope, policy makers need

Table 1. Conditions in the Development of Genetic Screening

Condition (Reference No.)	Role in Development of Genetic Screening	Disease Mechanism	Clinical Findings	Treatment Options	Genetics	Current Screening
Beta-thalassemia (2)	Pioneering carrier screening programs in the Mediterranean region	Reduced synthesis of hemoglobin beta chain	Severe anemia and hepatosplenomegaly, leading to failure to thrive (milder forms of disease occur with mutations causing milder impairment)	Transfusions and chelation therapy; bone marrow transplant	Autosomal recessive inheritance of mutations in the *HBB* gene	Carrier and prenatal screening
Cystic fibrosis (3)	First carrier screening guideline for nonminority population; first condition for which randomized controlled trial of newborn screening conducted	Abnormality in cystic fibrosis transmembrane conductance regulator function	Progressive loss of lung function related to thick lung secretions and recurrent infections; malnutrition; male infertility; increased risk of diabetes, pancreatitis, liver failure (milder forms of disease occur with mutations causing milder impairment; some mutations have variable effects)	Antibiotic and nutritional therapy; lung transplant	Autosomal recessive inheritance of mutations in the *CFTR* gene; >1,000 mutations identified, with different levels of functional impairment	Newborn screening, carrier and prenatal screening
Sickle cell disease (4)	Unsuccessful population-based carrier screening programs in the 1970s; carrier screening now offered in prenatal care; newborn screening initiated in the 1980s	Functional impairment of hemoglobin beta chain	Hemolytic anemia; vaso-occlusive events; increased risk of infections; clinical course variable	Fluids; pain management; transfusions; prophylactic antibiotic and hydroxyurea therapy; bone marrow transplant	Autosomal recessive inheritance of hemoglobin S or of hemoglobin S in combination with other beta-chain mutations	Newborn screening, carrier and prenatal screening
Neural tube defects (5)	First effort to develop prenatal maternal serum screening; first test offered to all pregnant women regardless of risk status	Unknown; results in failure to close neural tube during embryologic development	Variable neurologic impairment	Supportive care and symptom management	Multifactorial; genetic studies identify potential genetic contributors to risk	Prenatal screening
Phenylketonuria (6)	First newborn screening programs in the 1960s	Total or near-total deficiency of phenylalanine hydroxylase	Severe cognitive impairment (milder presentations occur for mutations causing partial enzyme deficiency)	Phenylalanine-poor, tyrosine-enriched diet	Autosomal recessive inheritance of mutations in the *PAH* gene	Newborn screening
Spinal muscular atrophy (7)	Most recent carrier screening recommendation	Degeneration and loss of lower motor neurons in the spinal cord and the brain	Progressive muscle weakness; different subtypes vary in age at onset and range of clinical manifestations	Supportive care and symptom management	Autosomal recessive inheritance of mutations in the *SMN1* or *SMN2* gene	Carrier and prenatal screening
Tay-Sachs disease (8)	First population-based carrier screening programs in the 1970s	Total or near total deficiency of hexosaminidase A	Neural degeneration beginning at 6 months; death by 4–6 years (milder presentations occur for mutations causing partial enzyme deficiency)	Supportive care	Autosomal recessive inheritance of mutations in the *HEXA* gene	Carrier and prenatal screening
Trisomy 21 (Down syndrome) (9)	First screening use of amniocentesis and prenatal chromosome studies	Unknown; chromosomal imbalance results in impairment	Cognitive impairment; increased incidence of congenital heart defects, hypothyroidism	Educational intervention; other surgical and medical therapy as indicated	Trisomy 21 (small percentage of cases due to chromosomal rearrangements resulting in partial trisomy 21)	Prenatal screening

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; HBB, hemoglobin, beta; HEXA, hexosaminidase A (alpha polypeptide); PAH, phenylalanine hydroxylase; SMN1, survival of motor neuron 1, telomeric; SMN2, survival of motor neuron 2, centromeric.

Table 2. Genome-scale Tests

Test (Reference No.)	Strengths	Limitations	Use in Clinical Management	Current or Proposed Screening Use
Array-based comparative genomic hybridization (14)	Rapid; adaptable to high throughput/automation; sensitive and specific when validated array used	Does not detect balanced chromosomal rearrangements	Evaluation of multiple congenital anomalies and developmental delay	Prenatal
Array-based single nucleotide polymorphism assessment analysis (12)	Rapid; adaptable to high throughput/automation; high sensitivity and specificity for measurement of specific gene variants	Choice of gene variants included in test determines value; current tests generally measure gene variants with low predictive value	No established clinical utility at present	Potentially useful if single nucleotide polymorphisms chosen for screening purposes
Whole genome sequencing (12, 15)	Comprehensive analysis; theoretically highest sensitivity; will detect both common and rare variants	Generates large amounts of uninterpretable data; high cost because of time- and expertise-intensive analysis; likely to reveal unwanted information	Likely a powerful diagnostic tool for enigmatic familial disorders	Could identify rare mutations for a wide range of disorders that benefit from intervention
Whole exome sequencing (12, 15)	High sensitivity; will detect both common and rare variants; fewer nonspecific findings than whole genome sequencing (but still a formidable problem); lower cost than whole genome sequencing	Less sensitivity than whole genome sequencing because of lack of analysis of noncoding regions of genome; otherwise, similar to whole genome sequencing	Likely a powerful diagnostic tool for enigmatic familial disorders	Could identify rare mutations for a wide range of disorders that benefit from intervention

explicit criteria to determine whether to add a test to the newborn screening panel. In an attempt to develop such criteria, the American College of Medical Genetics recommended a core panel of 29 conditions for newborn screening, most identifiable using tandem mass spectrometry technology (Table 3) (17). The report also recommended including an additional 25 conditions as ''secondary targets'' because they are part of the differential diagnosis for the 29 core conditions (Table 4). In developing these recommendations, the report considered 3 categories of evidence: clinical characteristics of the condition; analytical characteristics of the test; and options for diagnosis, follow-up, treatment, and management.

Because outcome data are limited or absent for many conditions, the analysis relied heavily on expert opinion and generated considerable debate (46, 47). Lack of data has been a persistent difficulty for newborn screening policy makers: the conditions in question are rare, making systematic observation difficult; and the clinical presentations often require immediate action, making implementation of clinical trials difficult and sometimes unethical (45, 48). However, the Secretary's Advisory Committee on Heritable Diseases in Newborns and Children endorsed the American College of Medical Genetics recommendations (49), as did other organizations concerned with child health (50, 51); most states now screen for the recommended conditions (Table 3).

Perhaps more importantly, the debate generated new approaches to evidence evaluation. The Secretary's Advisory Committee on Heritable Diseases in Newborns and Children commissioned an Evidence Review Group to assist the Committee in its appraisal of new candidate disorders (52). This multidisciplinary group performs systematic reviews of all available evidence (both published and unpublished) for candidate conditions. The Committee utilizes this analysis in making recommendations to states regarding the addition of new tests to newborn screening panels. In addition, the Eunice Kennedy Shriver National Institute of Child Health and Human Development has expanded efforts to support and implement research related to newborn screening (53).

Goals of newborn screening

The work of the Evidence Review Group, like the original phenylketonuria example that precipitated newborn screening, is anchored in traditional screening goals: identifying tests that enable early treatment to improve infants' health outcomes. However, growing test capacity has led to calls to expand not only the number of disorders screened for but also the goals of newborn screening. Several additional goals of newborn screening are proposed (54–56): parents may be spared the ''diagnostic odyssey'' that often occurs when a child has a rare disease; identification of the condition may allow for early initiation of supportive or palliative therapy when curative therapy is not possible; and because the diseases identified by tandem mass spectrometry are often genetic, early detection can inform future reproductive decisions. Finally, systematic identification of infants with rare diseases through population screening can enhance research to improve treatments.

Table 3. Incidence of Conditions Recommended for Universal Newborn Screening (Incidence in the US Population) (17, 18)

Amino acid disorders
Phenylketonuria (1:20,000)
Maple syrup urine disease (1:250,000)
Homocystinuria (1:250,000)
Citrullinemia (1:200,000)
Argininosuccinic acidemia (1:200,000)
Tyrosinemia type I (1:500,000)
Fatty acid oxidation disorders
Medium-chain acyl-CoA dehydrogenase deficiency (1:15,000)
Very long-chain acyl-CoA dehydrogenase deficiency (1:75,000)
Long-chain 3-OH acyl-CoA dehydrogenase deficiency (1:50,000)
Trifunctional protein deficiency (1:100,000)
Carnitine uptake defect (1:50,000)
Hemoglobinopathies
Sickle cell anemia (>1:5,000)
Hemoglobin S/beta-thalassemia (>1:50,000)
Hemoglobin SC (>1:25,000)
Organic acid disorders
Isovaleric academia (1:75,000)
Glutaric acidemia type I (1:100,000)
3-Hydroxy 3-methylglutaric aciduria (1:250,000)
Multiple carboxylase deficiency (1:250,000)
Methylmalonic academia (A, B) (1:100,000)
3-Methyl-crotonyl-CoA carboxylase deficiency (1:50,000)
Methylmalonic academia (Mut) (1:100,000)
Propionic acidemia (1:150,000)
ß-Ketothiolase deficiency (1:300,000)
Endocrine disorders
Congenital hypothyroidism (>1:5,000)
Congenital adrenal hyperplasia (>1:25,000)
Other
Biotinidase (>1:75,000 – lack of consensus)
Classical galactosemia (>1:50,000)
Hearing loss (>1:5,000)
Cystic fibrosis (>1:5,000)

If these goals were to become part of the rationale for newborn screening, they would alter the evidence required for new tests: Good analytic validity and a high predictive value would be sufficient, without any obligation to assess treatment benefit. This approach is controversial (57, 58). A white paper from the President's Council on Bioethics (58) concluded that mandatory screening programs should be limited to conditions that offer the opportunity to improve the health outcome of newborns. The Council recommended that newborn screening for other purposes be offered to parents as voluntary programs only.

An important corollary of this debate concerns communication about newborn screening. Testing is often implemented with minimal information provided to parents. Although most states provide informational brochures, many parents are unaware that their infant has been tested unless they are notified of a positive result (59, 60). As testing panels expand to include conditions with less time urgency or opportunity for definitive treatment, many argue that greater efforts are needed to inform parents, and potentially to obtain consent for screening (57, 59–62).

Challenges in evaluating newborn screening results

Policy discussions about the goals of newborn screening and associated communication strategies must take into account challenges in evaluating test results, including false-negative and false-positive results, ambiguities in the information provided by screening, and incidental findings. These challenges are common to all screening programs, but the nature of genetic information influences the form they take in newborn screening and other genetic screening.

False-negative and false-positive results. Newborn screening seeks to identify all affected infants, minimizing false-negative results. Thus, thresholds for quantitative traits are set to maximize sensitivity. False-negative results are also minimized by ensuring that the sample is collected at least 24 hours after birth, and some states collect a second sample 1–2 weeks after birth (19). This effort appears to be successful, in that false-negative rates for most conditions appear to be very low (63–66).

However, false-positive results are an inevitable feature of a screening process that seeks to maximize sensitivity. As more independent tests are added to newborn screening panels, the overall number of false positives increases (67). The definition of "false positive" varies across programs (68). For example, some states may designate a result that generates retesting of the same sample (without notification of the family) a false positive, while others categorize a false positive only if additional confirmatory testing is conducted; still others categorize any situation in which a repeat specimen is obtained from the child as a false positive.

Although false positives are an unavoidable part of the testing process, they must be managed to minimize harms from both an economic (e.g., cost of additional testing) and potential psychosocial impact. Anxiety, depression, and parent-child dysfunction may occur among parents of children who received false-positive results (Table 5) (69–71). Importantly, this anxiety appears related to poor parental understanding of newborn screening (70). Studying the psychosocial effect of false positives is complicated by both the process and content of communication between providers and parents, including the sense of urgency with which an initial positive result is reported. Relatively few studies have been reported. As a result, a number of unanswered questions remain about the type and scope of harms (Table 5).

Overdiagnosis. Overdiagnosis is an emerging challenge with particular importance for genetic screening. The term refers to a screening-based diagnosis in a person who is destined to remain asymptomatic or whose course is not changed by early diagnosis. The potential benefits and

Table 4. Incidence of Secondary Targets Recommended for Universal Newborn Screening (Incidence in the US Population) (17, 18)

Amino acid disorders
Benign hyperphenylalaninemia (1:30,000)
Defects of biopterin cofactor biosynthesis (1:250,000)
Defects of biopterin cofactor regeneration (1:500,000)
Hypermethioninemia (1:200,000)
Citrullinemia type II (1:200,000)
Tyrosinemia type II (1:500,000)
Tyrosinemia type III (1:250,000)
Argininemia (1:250,000)
Fatty acid oxidation disorders
Dienoyl reductase deficiency (1:2,000,000)
Carnitine palmitoyl-transferase Ia deficiency (1:300,000)
Carnitine palmitoyl-transferase II deficiency (1:250,000)
Carnitine/acyl-carnitine translocase deficiency (1:300,000)
Glutaric acidemia type II (1:250,000)
Medium/short-chain 3-OH acyl-CoA dehydrogenase deficiency (1:2,000,000)
Medium-chain ketoacyl-CoA dehydrogenase deficiency (1:2,000,000)
Carnitine/acyl-carnitine translocase deficiency (1:300,000)
Hemoglobinopathies
Variant hemoglobinopathies (>1:50,000)
Organic acid disorders
2-Methylbutyryl-CoA dehydrogenase deficiency (1:500,000)
2-Methyl-3-hydroxybutyric aciduria (1:1,000,000)
3-Methyl-glutaconic aciduria (1:200,000)
Methylmalonic acidemia (Cbl C,D) (1:100,000)
Isobutyryl-CoA dehydrogenase deficiency (1:100,000)
Malonic aciduria (1:500,000)
Other
Galactokinase deficiency (1:25,000)

harms of overdiagnosis are influenced by treatment options, as illustrated by 2 newborn screening examples.

Most state newborn screening programs test for medium chain acyl-CoA dehydrogenase deficiency (Table 3) (19). Epidemiologic data suggest that 25% or more of infants diagnosed with this deficiency by newborn screening will remain asymptomatic; however, treatment consists primarily of dietary measures and is estimated to prevent death or disability in another 20%–25% (72). Thus, most states have determined that overdiagnosis is an acceptable burden for medium chain acyl-CoA dehydrogenase deficiency. In contrast, newborn screening for Krabbe disease, a rare neurogenerative disorder, is controversial because the course is highly variable and the treatment (bone marrow transplant) may be life threatening (73). In New York State, where testing for Krabbe disease is mandatory, all children with positive newborn screening results for this disease are followed clinically, with transplant usually offered only to those with particularly severe biochemical and genetic phenotypes and/or those with clinical findings of Krabbe disease. However, even for those "high-risk" children for whom follow-up data are available, more than half have remained asymptomatic (73). These factors led the Secretary's Advisory Committee on Heritable Diseases in Newborns and Children to recommend against adding Krabbe disease to its recommended newborn screening panel (74).

The issue is an important one for genetic screening programs because the penetrance (or likelihood that an individual will have clinical manifestations of disease) is often incomplete for individuals with a disease-associated genotype. Therefore, screening for most genetic conditions will identify some individuals who would do well if their conditions had remained undetected.

Findings of uncertain significance. Newborn screening has a significant potential to yield indeterminate results. Some abnormal metabolite levels detected by tandem mass spectrometry have unclear clinical significance, and the introduction of DNA-based technologies in newborn screening can generate additional uncertainty. For example, most screening protocols for cystic fibrosis include DNA-based testing and yield some findings of uncertain clinical significance—that is, infants with genotypes not diagnostic of cystic fibrosis yet not clearly normal (Table 1). When the confirmatory test, a measurement of sweat chloride, is normal, the infant is assigned to an indeterminate category now referred to as "Cystic Fibrosis Transmembrane Conductance Regulator-related Metabolic Syndrome" (75). The prognosis for these infants is unclear, but a substantial proportion are likely to remain symptom free.

As with false-positive results, results of this kind can generate anxiety. Parents may also experience long-term concern because of the lack of a clear prediction about their child's prospects. An observational study of parents and health care providers coping with such uncertainties found that multiple health care interactions may occur without resolution, during which time the infant is perceived as neither sick nor fully well (76).

Incidental findings. Screening may also identify clinical findings unrelated to the screening goal. The most conspicuous example in newborn screening is the identification of carrier status for genetic conditions—that is, individuals with a single mutation for a condition (called autosomal recessive) that manifests only when 2 mutations are present. The carrier is healthy but has the potential to give birth to a child with the disease if her mate is also a carrier. The tests used to screen for sickle cell disease and cystic fibrosis identify both affected infants and carriers. Because the carrier state occurs more commonly than the disease, the majority of "positive" results are for carriers (77).

Knowledge about the carrier status of an infant may lead to further testing in the family, providing information for parents or other relatives regarding reproductive risks. Whether learning about a carrier state is a benefit or cost of newborn screening has been a matter of debate. Some have argued that newborn screening programs should report results on carrier status (78, 79) and that these findings represent an ancillary benefit of testing (54–56). Others

Table 5. Psychosocial Effects of False-Positive Results From Newborn Screening

Current Findings (Reference No.)	Knowledge Gaps
Parents experience increased anxiety between receiving an initial positive result and determination that the result is a false positive (69).	How can parents best be supported during this period?
Some parents develop persistent psychosocial distress (e.g., depression, anxiety, parent-child dysfunction) after receiving a false-positive result (70).	Which parents are at risk of developing persistent psychosocial distress?
	What proportion of parents of children who receive false-positive results are affected?
Poor understanding of the testing process is associated with persistent psychosocial distress (70).	What aspects of communication will optimize understanding?
Parents of children with false-positive results do not appear to utilize more health care services (71).	What are the short-term and long-term health outcomes of parental psychosocial distress after receipt of false-positive results?

argue that routine reporting of carrier results violates the right ''not to know'' and is of no direct benefit to the infant (80). Furthermore, offering carrier results without prior counseling or the opportunity for informed consent is contrary to current clinical practice (62). State practices vary regarding notification of parents about carrier status, reflecting the unresolved debate about expanded goals for newborn screening (77).

Implications of genome-scale tests. The debate regarding expanded goals is likely to intensify as new technologies are developed. Newborn screening currently utilizes DNA-based testing in a limited fashion—for example, as a confirmatory test in some screening protocols for cystic fibrosis. However, as costs decrease, new genome-scale tests (Table 2) may be applied to newborn screening. Some experts advocate moving toward this approach as a means to achieve more comprehensive identification of infants with genetic disorders (54). Using genome-scale tests in newborn screening would, however, greatly expand identification of carriers of genetic diseases, the risk of overdiagnosis, incidental findings such as genetic susceptibilities to common adult-onset disorders, and findings of uncertain significance.

REPRODUCTIVE GENETIC SCREENING

In contrast to newborn screening, reproductive genetic screening occurs in clinical settings, usually as part of obstetric care. Two types of reproductive genetic screening are in routine use: tests during pregnancy to identify fetuses with trisomy 21 or neural tube defects (Table 1), and carrier tests to identify couples at risk of having children with specific autosomal recessive conditions. Screening is performed not to implement therapy but to allow parents the opportunity to terminate (or avoid) a pregnancy to prevent the birth of an affected child. Social concerns, in particular, parents' reproductive autonomy and physicians' interests in avoiding litigation, have played an important role in the development of these screening programs.

Because the decision to terminate a pregnancy is highly personal and societally controversial, experts characterize prenatal and carrier tests as optional, in sharp contrast to mandated newborn screening. In keeping with this difference, genetics professionals have developed a counseling approach that avoids recommendations about testing and instead has the goal of assisting couples to determine their own preferred course of action (81, 82). Genetics professionals have also helped to justify reproductive genetic services by de facto practice norms that seek to limit reproductive testing to early-onset diseases that cause severe, untreatable impairment (83–85). Case reports of prenatal testing for other purposes—for example, for sex selection (86) or to assure a sibling match for organ donation (83)—demonstrate the willingness of some to push beyond these boundaries, but these uses of genetic testing have not been part of routine prenatal screening.

Even when limited to severe childhood-onset conditions, prenatal screening raises questions both because abortion is controversial and because judgments differ regarding the severity of conditions for which prenatal screening is offered. Disability advocates argue that selective abortion of fetuses with disorders such as trisomy 21 brings 2 social harms: it deflects attention away from the needs of people living with disabilities and it implies a diminished social value for such individuals (87). Some advocates consider any use of selective pregnancy termination morally objectionable. Others support the right of individuals to make autonomous decisions about pregnancy termination, but they argue that prospective parents have a right to receive complete and balanced information about persons with disabilities, including their potential for a good quality of life, to ensure that decisions are not based on inappropriately negative views of genetic disorders.

Historical background: prenatal screening for trisomy 21

Prenatal identification of trisomy 21 was reported in 1970 (84), utilizing genetic analysis of fetal cells derived from amniotic fluid (88). With the legalization of abortion and the recognition of an increasing risk of trisomy 21 with maternal age (89), prenatal screening for trisomy 21 became an accepted practice for women of ''advanced maternal age'' (90). Lawsuits claiming ''wrongful birth'' also had an impact on practice standards. These suits claim harm based on the failure to offer prenatal testing to a pregnant women who subsequently gives birth to a child with a genetic disorder (91, 92); in essence, they are malpractice claims, arguing a failure to disclose information pertinent to prenatal care. Wrongful birth suits are frequently successful in the United

States, in contrast to the more controversial claim of ''wrongful life,'' in which the child, as plaintiff, claims she or he should not have been born (92).

In the early 1970s, researchers in the United Kingdom found an association between elevated levels of alpha-fetoprotein in maternal blood and fetal neural tube defects (Table 1), suggesting that screening for alpha-fetoprotein in maternal blood could be used to detect pregnancies at higher risk of neural tube defects (93). Ultrasound could then be used to determine whether a neural tube defect was present. As with trisomy 21, legal considerations played a role in establishing routine prenatal screening for alpha-fetoprotein in maternal blood. In 1985, lawyers for the American College of Obstetricians and Gynecologists noted that more than 100,000 women in the United States had undergone this type of testing and advised their membership that this level of use suggested malpractice jeopardy if a clinician did not offer testing (94). This legal alert was considered tantamount to making screening for alpha-fetoprotein in maternal blood standard of care in prenatal medicine (95).

The observation of an association between low levels of alpha-fetoprotein in maternal blood and fetal trisomies such as trisomy 21 (96) offered a second rationale for maternal serum screening, as well as the opportunity to expand trisomy 21 screening to younger women. Alpha-fetoprotein in maternal blood alone had only limited predictive value, but further research identified a panel of maternal serum measures that provided reliable identification of pregnancies at increased risk of trisomy 21. Current US obstetric practice includes the offer of such screening in all pregnancies (97).

Historical background: carrier screening

Concurrent with the development of prenatal screening programs, community-based carrier screening programs were developed among populations with an increased incidence of specific genetic diseases (77). The first carrier screening program, for Tay-Sachs disease (Table 1), was made possible by the discovery of the underlying biochemical deficit (98). Over a 5-year period from 1971 to 1976, Tay-Sachs disease carrier screening programs were implemented in Jewish communities in more than 50 US cities (85). Several factors contributed to this process, including the high rate of carriers in Jewish populations (Table 1), advocacy on the part of scientists/clinicians who were deeply involved with at-risk families, and the existence within the Jewish community of organizations willing to help coordinate early testing programs (85). Many early screening programs were implemented in synagogues or other community centers. By 1977, prenatal diagnosis for Tay-Sachs disease had been performed in an estimated 461 pregnancies (85). Of these, 371 involved couples with a previous affected child, and 90 involved couples identified by Tay-Sachs disease carrier screening, resulting in identification of Tay-Sachs disease in 118 pregnancies. Elective pregnancy termination occurred in 93 of 97 pregnancies of couples with a previously affected child and in 21 of 21 pregnancies in couples identified by carrier screening.

Tay-Sachs disease carrier screening served as a model for screening programs in the Mediterranean region to identify beta-thalassemia carriers (Table 1). These programs, like those for Tay-Sachs disease, were community based, focused on a genetic disease with increased prevalence, and resulted in dramatic reductions in births of affected children through pregnancy termination (99). As with Tay-Sachs disease, carrier screening received strong community support and incorporated access to genetic counseling, prenatal diagnosis for couples at risk, and abortion services (99–101).

Carrier screening for sickle cell disease was also begun in the 1970s in US African-American communities, but this effort was ultimately viewed as a failure. There are likely many contributors to this outcome, including racial tensions, discriminatory insurance practices directed at sickle cell disease carriers, testing procedures that failed to distinguish between carriers and those with the disease, and problematic screening procedures (102–104). For example, many programs screened school-age children under legislative mandates; educational, counseling, and follow-up procedures were often weak and sometimes absent; and many screening programs were initiated without community involvement or support. In addition, prenatal diagnosis was not yet an option when sickle cell disease carrier screening programs were initiated (105); by comparison, the availability of prenatal diagnosis and the option to terminate affected pregnancies was seen as a central element in the success of carrier screening programs for Tay-Sachs disease and beta-thalassemia (85, 99).

Carrier testing before pregnancy

Although most carrier screening programs have been focused on identifying carrier couples for prenatal diagnosis (and the option of pregnancy termination), there has always been interest in offering carrier testing before pregnancy. Preconception testing offers couples a wider range of reproductive options if they wish to prevent the birth of an affected child: they can choose not to have children, or, if they have access to the technology, they can choose sperm donation or in vitro fertilization utilizing either egg donation or preimplantation genetic diagnosis. Carrier testing prior to mate selection can also provide carriers the opportunity to choose a partner who is not a carrier to avoid reproductive risk, but this approach has been implemented only in rare social circumstances (106).

Practice guidelines

As reproductive genetic screening became established, it influenced practice standards, particularly obstetrics practice (97, 107–113). Most practice guidelines for carrier screening continue to be directed toward population groups at highest risk of specific genetic diseases, requiring health care providers to make judgments about which patients are candidates for screening. For example, screening for Tay-Sachs disease carriers is generally performed as part of a testing panel offered to women of Ashkenazi descent. In its most recent practice guideline on Tay-Sachs disease screening, the American College of Obstetricians and Gynecologists recommends that Jewish women be screened for Tay-Sachs disease and 3 additional conditions more

prevalent in people of Ashkenazi descent (107). Both the U.S. Preventive Services Task Force (108) and the American College of Obstetricians and Gynecologists (109) recommend hematologic screening in early pregnancy to detect beta-thalassemia, sickle cell disease, and other hemoglobinopathy carriers among patients at risk, as defined by race/ethnicity (African American, African, Mediterranean, and southeast Asian).

Recent additions to carrier screening recommendations

Carrier screening is currently recommended for 2 additional conditions: cystic fibrosis and spinal muscular atrophy (110–114). Screening for cystic fibrosis carriers is based on a small subset of mutations in the cystic fibrosis transmembrane conductance regulator gene, *CFTR*, from more than 1,000 so far documented that are the most common in the population (111–113). In 2001, the American College of Obstetricians and Gynecologists and the American College of Medical Genetics (110–112) recommended that cystic fibrosis carrier screening be ''offered'' to non-Hispanic European Americans, for whom carrier detection is greater than 85%, and ''made available'' to patients of other ethnicities. This recommendation reflected the higher prevalence of cystic fibrosis in people of northern European descent and the limited sensitivity of the screening panel in most other ethnic groups. However, the recommendation posed difficulties for health care providers; an American College of Obstetricians and Gynecologists survey found that few of its members used ethnicity in deciding whether to offer cystic fibrosis carrier testing (115). In a 2005 update, the American College of Obstetricians and Gynecologists endorsed offering screening to all couples regardless of race or ethnicity (112). Carrier screening for spinal muscular atrophy (Table 1) is also recommended for all racial and ethnic groups (113).

Effect of reproductive genetic testing on disease incidence

Reduction of disease incidence has been an explicit goal of some carrier screening programs, including those for Tay-Sachs disease and beta-thalassemia (85, 99). In current practice guidelines, however, the emphasis is on offering parents reproductive choices and on the voluntary nature of testing (107–114). Nevertheless, population data on cystic fibrosis and trisomy 21 suggest that an effect on incidence can be seen even when it is not an explicit goal of screening (Tables 6 and 7). Several studies have found reductions in cystic fibrosis births associated with genetic screening (Table 6) (116–121). One study observed a significant decrease in incidence of cystic fibrosis births in a region of Italy where population-based carrier screening is offered, but not in a contiguous region where carrier testing is more limited (121). The decrease could not be fully explained by documented instances of pregnancy termination and therefore could reflect other effects of knowledge about carrier status, such as avoidance of pregnancy.

The story is more complicated for trisomy 21 (Table 7) (122–130): while pregnancy termination has reduced trisomy 21 births in many regions, a trend toward increasing maternal age has also been observed. Because trisomy 21 increases with maternal age, the net effect on trisomy 21 incidence has been variable.

Effect of technology development

As with newborn screening, genome-scale tests are likely to have important effects on reproductive genetic screening. Prenatal array-based comparative genomic hybridization (Table 2) is currently being used to evaluate abnormal fetal ultrasound findings, and in some instances has been offered to older pregnant women as a screening test (131, 132). The test has higher sensitivity than previous chromosomal tests but can also identify genetic changes of uncertain significance; for this reason, its use in prenatal screening is debated (133). A new technique, extraction of fetal DNA from maternal serum (134), is also likely to cause debate because it creates a noninvasive method to accomplish prenatal testing for a wide array of genetic conditions.

Genomic technology will also have an impact on carrier testing: assessment of multiple carrier states will become increasingly feasible, and, as tests become more comprehensive, tailoring testing to ethnicity will no longer be necessary (135). A prototype of a genome-scale carrier test has been described, in which sequencing technology was used to identify carrier states for 448 recessive childhood diseases (136). Although the test was successful in identifying carriers, it also generated results that could not be fully interpreted—for example, gene variants that could reflect either a carrier state or normal variation. In addition, study data indicated that 122 of 460 mutations identified as disease associated in previously published studies were in fact normal variation. These findings indicate the need for a substantial research investment to generate accurate clinical tests from emerging genomic technology.

As genome-scale tests become sufficiently accurate for clinical use, preconception screening may become a more viable component of reproductive genetics. Comprehensive carrier assessment could involve a single test that could be administered in a primary care setting. The test could also combine carrier screening with other assessments of genetic susceptibility—for example, tests for cancer or other common disease susceptibility—to guide prevention efforts. This approach would blur the line between reproductive genetics and the use of testing to predict risk or guide health care in a way that parallels the call for expanded goals of newborn screening (54).

GENETIC SCREENING AS A COMPONENT OF PRIMARY CARE

No DNA-based tests are routinely incorporated into primary care practice. However, screening for genetic risk is widely recommended in the form of family history assessment. An initiative of the US Surgeon General, supported by the Centers for Disease Control and Prevention and many professional organizations, urges individuals to learn their family history and discuss it with their health care providers: ''Tracing the illnesses suffered by your parents,

Table 6. Genetic Screening and the Incidence of Cystic Fibrosis[a]

Location, Years, and Population (Reference No.)	Genetic Screening Context	Sources	Findings
Massachusetts, 1999–2006, newborns in Massachusetts (116)	Newborn screening for cystic fibrosis in place throughout the study period; recommendations for population-based cystic fibrosis carrier screening introduced in 2001	Data from newborn screening records	Incidence of cystic fibrosis births lower in 2003–2006 compared with 1999–2002 ($P < 0.005$)
Brittany, France, 1990–2005, newborns and women receiving prenatal genetic testing in Brittany (117)	Newborn screening for cystic fibrosis in place throughout the study period; prenatal testing for cystic fibrosis available to at-risk couples	Data from newborn screening records and specialty center records	Stable cystic fibrosis birth incidence (1/3,153 in 1990–2000, 1/3,188 in 2000–2005); 163 cystic fibrosis pregnancies terminated; estimated 30% lower cystic fibrosis birth incidence as a result of pregnancy termination
Victoria, Australia, 1979–2006, newborns and women receiving prenatal genetic testing in Victoria (118)	Newborn screening for cystic fibrosis introduced in 1989; increased availability of prenatal testing for cystic fibrosis for at-risk couples after 1989	Data from 3 cystic fibrosis specialty centers, newborn screening records, and specialty center records	Cystic fibrosis livebirths: 3.96/10,000 in 1979–1988 and 3.28/10,000 in 1980–2006 (reduction of 17%, $P = 0.025$); number of prenatal tests for cystic fibrosis: 10 in 1979–1988 (3 cystic fibrosis pregnancies, all terminated), 304 in 1980–2006 (76 cystic fibrosis pregnancies, 70 terminated)
Canada, 1971–2000, people with cystic fibrosis in Canada (119)	Prenatal testing for cystic fibrosis available in 1989	Nonparametric model of cystic fibrosis birth rates, from Canadian Cystic Fibrosis Foundation data registry and Canadian vital statistics	Estimated cystic fibrosis birth rates stable at 1/2,714 from 1971 to 1988; subsequently, birth rates followed a linear decline to 1/3,608 in 2000
The Netherlands, 1961–1965, 1975–1994, people with cystic fibrosis in the Netherlands (120)	Prenatal testing available starting in 1990	Survey of all living cystic fibrosis patients; additional data from cystic fibrosis mortality statistics and birth records	Birth prevalence: 1961–1965: 1/3,600, 1974–1994: 1/4,750; % of infants with 1 non-Western parent increased from 1% in 1972 to 16% in 2000
Northeast Italy, 1993–2007, newborns in northeast Italy (121)	Newborn screening for cystic fibrosis in place throughout the study period; population-based cystic fibrosis carrier and prenatal testing available in the eastern region of northeast Italy; these services provided for only at-risk parents and assisted reproduction in the western region	Data from newborn screening records and specialty center records	A mean annual decrease in cystic fibrosis births of 0.16/10,000 observed; reduction significantly greater in the eastern than in the western region and inversely related to the number of carrier tests performed

[a] Relevant articles were identified in 3 searches of the PubMed database using the terms "cystic fibrosis," "incidence," and "screening" in combination with "newborn," "carrier," or "genetic*"; the searches were limited to articles published in English from 2000 to 2010. Articles were selected if they provided data on cystic fibrosis birth incidence and use of genetic screening, provided data on time trends in cystic fibrosis birth incidence, and derived data from a defined geographic location or health care system. A total of 132 articles were identified; 7 met inclusion criteria. Two articles presented data from the same region (Brittany); the article with more complete incidence data was used.

grandparents, and other blood relatives can help your doctor predict the disorders to which you may be at risk and take action to keep you and your family healthy" (137). This initiative is in keeping with long-standing practice standards that define family history as an essential component of a full patient evaluation.

The scientific basis for using family history as a risk assessment tool is weak, however. Although family history has been documented as a risk factor for numerous diseases, a National Institutes of Health State of the Science evaluation found limited evidence to guide its use in clinical practice, particularly to prevent common complex diseases (138). The evaluation panel concluded that research is needed to define systematic methods for obtaining family history, evaluate the use of family history to guide interventions, and assess outcomes.

Despite these cautions, family history is already incorporated in numerous practice guidelines. For example, the U.S. Preventive Services Task Force recommends that family history of breast and ovarian cancer be used to identify women who are appropriate candidates for breast cancer gene (*BRCA*) testing (139). Similarly, guidelines for colorectal cancer screening utilize family history in identifying candidates for genetic testing and determining the appropriate age to begin screening (140), and family history is used as a factor in the initiation of cholesterol-lowering therapies (141). These examples build on decades of epidemiologic observation (142).

Table 7. Genetic Screening and the Incidence of Trisomy 21[a]

Location, Years, and Population (Reference No.)	Genetic Screening Context	Sources	Findings
South Australia, 1982–1996, women who gave birth or terminated pregnancy with trisomy 21 (122)	Maternal serum screening introduced in 1992; prior to that time, prenatal testing for trisomy 21 offered to pregnant women >34 years of age	Data from public health databases (pregnancy outcomes, pregnancy terminations, birth defects registry) and from hospital records	During the study period, trisomy 21 births decreased from 1.05 to 0.42/1,000 livebirths; use of prenatal testing for trisomy 21 increased from 5.8% in 1991 to 10.1% in 1996.
Denmark, 2000–2007, pregnant women and children born during the study period in 19 Danish departments (123)	First-trimester trisomy 21 screening introduced in 2004–2006, combining assessment of maternal serum markers, ultrasound findings, and maternal age	Data from public health databases (birth data, cytogenetics registry)	Trisomy 21 births decreased from 55–65/year in 2004–2005 to 31/year in 2005 and 32 in 2006.
Atlanta, Georgia, 1990–1999, pregnant women and children born during the study period in the Atlanta metropolitan region (124)	Both prenatal testing for pregnant women >34 years of age and maternal serum screening available during the study period	Data from hospital sources only (1990–1993) or hospital and perinatal offices (1994–1999)	Trisomy 21 incidence in 1990–1993: 8.4/10,000 livebirths when terminations were excluded and 8.8/10,000 livebirths when terminations were included; incidence in 1994–1999: 10.1/10,000 livebirths when terminations were excluded and 15.3/10,000 livebirths when terminations were included.
Paris, France, 1981–2000, pregnant women, and children born during the study period (125)	Start of reimbursement for prenatal testing following abnormal ultrasound in 1989; start of widespread serum screening for trisomy 21 in 1996	Data from the Paris Registry of Congenital Anomalies, state birth records	Incidence of trisomy 21 births decreased 3%/year despite increasing average maternal age during the time period.
Eastern Switzerland, 1980–1996, pregnant women, and children born during the study period (126)	Prenatal testing for trisomy 21 available during the study period	Data from cytogenetic laboratories for women residing in eastern Switzerland, state birth records	During the study period, trisomy 21 births remained constant, average maternal age increased, and prenatal detection of trisomy 21 increased.
Singapore, 1993–1998, pregnant women, and children born during the study period (127)	Prenatal testing for trisomy 21 available during the study period	Data from public health databases (registry of births and deaths) and hospital, clinic, and laboratory records	Trisomy births decreased from 1.17 to 0.89/1,000 livebirths during the study period; decrease could be accounted for by increased prenatal detection and pregnancy termination.
South Belgium, 1984–1989 and 1993–1998, pregnant women receiving prenatal genetic testing (128)	Maternal serum screening introduced in 1990–1991; all prenatal testing performed at centralized genetic centers	Data on prenatal testing and pregnancy outcome from genetic center records	In 1984–1989, 244 trisomy 21 cases were detected (1/876 pregnancies), 17% prenatally; in 1993–1998, 294 trisomy 21 cases were detected (1/704), 56% prenatally; more than 90% of prenatal trisomy 21 cases were terminated, for an estimated shift in birth incidence from 1/794 to 1/1,606.
Czech Republic, 1996–2007, children born during the study period (129)	First-trimester screening for trisomy 21 implemented during the study period	Data from national registry of congenital anomalies	Trisomy 21 births/10,000 births decreased from 5.42 in 1996 to 3.66 in 2007, with a corresponding increase in first-trimester prenatal testing.
Croatia, 1996–2005, pregnant women, and children born in the Primorsko-goranska region (130)	Maternal serum screening and prenatal testing for women >34 years of age available during the study period	Data from public health databases and regional specialty centers	The trisomy 21 birth incidence was 1.4 per 1,000 livebirths for the study period; a decreasing trend was observed over the study period but was not significant; 34% of pregnant women had maternal serum screening, and 12% of women >34 years of age had prenatal trisomy 21 testing.

[a] Relevant articles were identified in 2 searches of the PubMed database using the terms "trisomy 21" or "Down syndrome" in combination with "incidence" and "prenatal." The searches were limited to articles published in English from 2000 to 2010. Articles were selected if they provided data on trisomy 21 birth incidence and use of genetic screening, included data on time trends in birth incidence of trisomy 21, and derived data from a defined geographic location or health care system. A total of 361 articles were identified; 9 met inclusion criteria. An additional article was identified from references of the selected articles. Two articles provided data from the same region (Victoria, Australia); the more recent article was used.

Table 8. Binning Information From Genome-scale Tests

Bin	Example
1. Medically actionable conditions or risks	Identification of cancer susceptibility or increased risk of adverse reaction to a specific drug
2. Gene variants associated with clinical outcome, not medically actionable	Identification of small increased risk in common disease susceptibility that does not change general prevention recommendation (e.g., small increased risk of diabetes)
3. Gene variants with only reproductive implications (no health risks for carrier)	Identification of carrier status for severe genetic disease
4. Gene variants that provide potentially sensitive information, not medically actionable	Identification of increased risk of dementia or mental illness
5. Gene variants of unproven, unknown, or unclear clinical significance	Most data derived from whole exome sequencing, whole genome sequencing, and current analysis of single nucleotide polymorphism microarray

Cascade genetic screening offers an adjunct to family-based risk assessment. This term refers to screening of family members after an individual is diagnosed with genetic disease. For example, screening family members after an initial diagnosis of inherited colorectal cancer syndrome substantially increases the benefit of the initial diagnosis (143). This approach offers a means to increase detection of rare conditions when universal screening is not feasible or economically viable (144).

The association between family history and disease risk undoubtedly captures the effects of both heredity and shared environment and of complex gene-environment interactions. It is likely, however, that family history often functions as a rough proxy for genome-scale tests, identifying genetic susceptibilities via a positive family history. Advocates for expansion of genetic screening anticipate that DNA-based tests may offer better ways to identify actionable risks (12, 16).

THE FUTURE OF GENETIC SCREENING: GENOME-SCALE TESTING

Different genome-scale tests have specific strengths and limitations (Table 2), but all provide information about multiple genetic risks and carry the potential for discovering information that is confusing and difficult to interpret. Effective use of these tests in clinical care will require substantially more data correlating genetic variation with health outcomes, but, as the clinical implications of genomic data are understood, these technologies offer mechanisms for universal screening. Early prototypes of this approach are already being reported (136, 145); they point to important challenges that have been foreshadowed by newborn screening and carrier screening.

Making sense of complex data

Extensive sequencing procedures—such as whole exome sequencing and whole genome sequencing (Table 2)—are intrinsically broad in scope, identifying gene variants associated with both severe and mild, treatable and untreatable conditions. They also provide much information that is ambiguous or uninterpretable. Over time, some of the ambiguity will lessen as more is learned about associations between genetic variation and disease. However, most genetic contributors to health and disease are part of a complex etiology involving environmental exposure and social determinants; genomic prediction will always be incomplete.

Genome-scale tests therefore raise critical questions about how tests are offered and results reported. A recent report of clinical counseling following whole genome sequencing performed in a research study (145) illustrates the complexity of interpreting and communicating whole genome sequencing findings. An individual underwent whole genome sequencing as part of a research study and subsequently worked with a team of colleagues to determine the health implications of the results. A key—and expected—finding was the large volume of information: 2.6 million single nucleotide polymorphisms and 752 copy number variants were identified (145). The team decided to focus its analysis on genes associated with inherited disease, novel gene variants, variants known to be associated with drug response, and variants known to be associated with common disease risk. Consultation with multiple databases and the published literature was required. The team developed an innovative, but resource-intensive, approach for estimating common disease risk, in which pretest risk was assessed using conventional risk factors, to determine the degree to which risk changed as a result of whole genome sequencing.

This extensive analytic effort yielded a variety of findings: gene variants of high and limited penetrance, carrier status for several autosomal recessive diseases, more than 60 gene variants associated with drug response, and altered risk for 8 of 55 common diseases. Despite this wealth of information, much of the data remained uninterpretable (136).

Making use of whole genome sequencing data: the binning concept

One approach to the diversity of information provided by whole exome sequencing or whole genome sequencing would be to define ''bins'' for different types of information; a potential schema for doing so is shown in Table 8. From a traditional screening perspective, only a subset of bin 1 findings would be considered for inclusion in a screening test—those for which medical action is effective at an early, asymptomatic stage. The history of genetic screening suggests that there would also be strong interest in

screening for gene variants associated with reproductive risk (bin 4).

There are many challenges to the binning approach: consensus procedures would be needed to determine bin assignments, and different stakeholders would likely debate what constitutes medically actionable information. Methods for storage of whole genome sequencing data and appropriate retrieval of results for different clinical purposes would be required. Over time, the information in the last bin—uninterpretable data—would be expected to diminish, while the gene variants associated with opportunities for treatment (bin 1) would increase, and methods for updating bin assignments would be needed.

The binning concept provides a framework for utilizing whole genome sequencing and similar genome-scale information in a way that is consistent with current screening practice. In essence, this approach would call for test design, interpretation, and reporting procedures that serve specific screening purposes. For example, array-based tests could be designed to assess gene variants associated with drug response or with risk of specific health problems, such as cancer. A test based on sequencing technology could also achieve a targeted purpose if the analysis focuses on specified genes, as is the case in the prototype carrier test based on sequencing technology (136). Targeted tests of this type could serve a screening purpose in primary or specialty care if they were designed to inform specific preventive care questions, such as when to initiate different types of cancer screening.

As with the debate about disclosure of carrier tests and other incidental findings in newborn screening, however, the ethical implications of withholding information that would otherwise be available from the test (55, 56)—or imposing it and depriving an individual of the right not to know (62, 80)—would have to be considered. More fundamentally, debate is needed about the appropriate use of whole genome sequencing or similar genome-scale tests as screening tools.

Policy implications

From the perspective of screening policy, the most challenging effect of burgeoning genomic technology is the way in which it has led some to question the traditional goals of screening. Similar to the introduction of tandem mass spectrometry in newborn screening, but on a much larger scale, genome-scale tests may increasingly be used to justify a different approach to screening—one that seeks to inform individuals about all their genetic traits and susceptibilities. Many will likely view this technology as offering a new way to think about the screening process—as a source of valued information with many different potential purposes, not limited to the purpose of early detection to improve health outcome. Some commentaries already suggest that whole genome sequencing and other genome-scale tests might be used as a fundamental measurement tool, more akin to a physical examination than a screening test (12, 15, 16, 145).

Whether this approach is desirable will require both research and considered judgment. In particular, empiric research is needed to define the harms associated with overdiagnosis, false-positive and false-negative results, and the other incidental findings that will inevitably accompany screening by genome-scale tests (146). As the benefits and harms are clarified, there will also be a need for careful deliberation about the use of genome-scale screening on the part of all concerned, including genomic researchers, clinicians, public health officials, health care payers, and, most importantly, potential recipients of this novel screening approach.

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