Genomic Screening: The Mutation and the Mustard Seed

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A mutation, like a mustard seed, is minuscule. The mustard seed as a metaphor for tiny things that grow stunningly in significance entered the lexicons of many cultures two millennia ago through its mention in the New Testament of the Bible. The mustard seed metaphor is apt for application to mutation detection by genomic screening. Each mutation is a seed that shoots its roots down, burrowing its way into ancestral generations, while also arborizing upwards into a family tree with many branches.

The mustard seed appears in a biblical parable, a simple story that is supposed to prompt deep reflection and impart a moral lesson. The obvious significance of the mustard seed is that the greatest things may grow from the smallest. However, as Pliny the Elder wrote of the mustard seed, "… on the other hand, it is extremely difficult to rid the soil of it when once sown there, the seed when it falls germinating immediately."[1] No seed should be planted unless its planters know what will grow from it, how far it will spread, and what effects it will have on the broader ecosystem, now and in the foreseeable future.

In this paper, I will argue that genomic screening is proceeding too rapidly, too broadly, and without due consideration and control of its ramifications for families and for the global clinical ecosystem. Genomic screening can potentially save lives, so one might argue that it could not possibly proceed rapidly enough. However, we must consider the safety and acceptability as well as efficacy of any medical intervention. Four aspects of safety and acceptability are currently lagging too far behind the rapidly advancing leading edge of genomic screening: (1) informed consent, genetic counseling, cascade genetic testing, and medical management of at-risk relatives; (2) availability of clinically valid data for safe, accurate mutation interpretation; (3) effective health systems to improve outcomes of asymptomatic people who screen positive for mutations; (4) assessment and minimization of potential social harms. Therefore, genomic screening should be kept small-scale, focused, and contained within closely monitored research protocols until ethical, effective family genetic counseling systems are established and the availability of effective treatment of at-risk patients is assured.

Genomic Screening: Process and Progress

Genomic screening, as I used the term here, is sequencing of portions or all of the human genome to detect pathogenic mutations for predictive rather than diagnostic purposes. The quest for diagnosis of rare genetic syndromes was the initial, primary rationale for the implementation of clinical genome or exome sequencing (CGES), and it has been highly successful for that purpose.[2] However, the earliest instances of genomic screening arose from what were initially termed "incidental findings" of diagnostic CGES done for a compelling reason that justified a broad search for known or presumed pathogenic mutations in many Mendelian disease genes.

The American College of Medical Genetics and Genomics (ACMGG) released guidelines on reporting of incidental findings that sparked passionate, enlightening, but still unsettled debate despite the release of revised recommendations.[3] The implications of genomic screening for genetic counseling of family members were explicitly considered in the debate. However, in the small,

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relatively insular community of clinical genetics professionals, it appears to have been generally assumed that the existing genetic counseling system could, at least at first, probably absorb the relatively small proportion (~1%) of patients screening positive for the current list of 59 medically actionable mutations predisposing to cancers or to cardiovascular conditions.[4] When performed on a small scale, cascade genetic counseling and mutation screening within extended families almost always concludes after a modest number of individuals are contacted, as branches of the family either are estranged or have no close living relatives, and a particular mutation will typically "peter out" in future generations just as surnames "daughter out" from a patrilineage. Thus, such counseling and screening have heretofore been challenging but manageable in clinical genetics.

However, the growth of genome sequencing capacity has outpaced Moore's law (biennial doubling of transistor number in densely integrated computing circuits).[5] Sequencing costs have plummeted; direct-to-consumer access to exome sequencing is now available for under $500, and preventive genomics clinics are beginning to form to serve patients whose presenting complaint is not a sign or symptom but an exome test result.[6] Thus, access to CGES is no longer confined to a circumscribed group of mostly pediatric patients with "mystery diagnoses." Despite efforts to scale genetic counseling using computerized decision support tools, such counseling is often highly particular to individual patients and not easily scalable, and cascade screening of family members is an arduous task because it involves geographical dispersion and highly complicated relationships.

Numerous genotype-phenotype biobanks and longitudinal projects have been established,[7] and their findings will be invaluable for informing genomic screening implementation discussions and debates. Key ethical requirements of such experimental precision medicine pilot projects include: informed consent; detailed scientific protocol with limited, targeted return of particular, pre-selected genetic results to participants expressly for screening purposes; multidisciplinary expert oversight and longitudinal tracking of medical and psychosocial outcomes; institutional infrastructure capable of handling harms that may arise; and the expectation of timely, transparent, peer-reviewed publication of results, often as a condition of grant funding.

It is important to note that direct-to-consumer provision of broad sequencing data to individuals lacks the foregoing comprehensive ethics package. Targeted return of particular results of genomic sequencing to patients whose clinical characteristics make them appropriate for screening in the context of a research program could be a valuable contribution to generalizable knowledge. In contrast, untrammeled return of any and all genetic information to genomic research participants would lack essential ethical safeguards, and the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard has recently released principles and a toolkit for return of individual research results to clinical trial participants.[8]

However, reporting on the 2017 Precision Medicine Conference recently, GenomeWeb reporter Barbara Heger wrote, "As a number of studies have already demonstrated, people want their genetic data, and so far it seems that returning that data has not had negative consequences on participants."[9] Also at that conference came the first claim of a life saved by systematic genomic screening in a large health system. David Ledbetter of Geisinger Medical Center related a case of exome sequencing detecting a BRCA mutation in a 57-year old woman without known family history of breast or ovarian cancer who underwent prophylactic surgery that detected a fallopian tube tumor. This was touted as a "likely life saving" consequence of genomic screening. If so, it was a great moment in the short history of genomic screening. However, BRCA is one gene that has been considered a prime candidate and bellwether for genomic screening for decades, yet evidence is still lacking for BRCA screening in the general population.[10]

It is important to note that initial results of the Geisinger BRCA screening study also led to detection of cancers so small that they were not seen on screening mammograms in a couple of female patients.[11] Also detected was a male with a BRCA2 mutation who turned out to have prostate cancer. Given that small, indolent breast or prostate cancers are highly prevalent, and that most do not progress clinically, genomic screening does not necessarily save lives in such cases.[12] However, it definitely leads to medical evaluation and treatment, with its attendant costs and risks. Though germline genomic mutations have the advantage of being static biomarkers, as compared to dynamic biomarkers such as mammography or prostate specific antigen, the challenges of screening healthy people remain equally formidable regardless of biomarker choice. Systematic evidence of risks and benefits should be obtained before genomic screening "goes viral" in large segments of the general population. As James Evans of the University of North Carolina has stated,[13] the public "shouldn't be seduced by the occasional cherry-picked case reports."

The Genetic Counseling Gap

Genetics poses special problems due to the segregation of germline mutations in families. This is concerning, as what is most conspicuously absent from published discussions of virtually all recent genomic screening initiatives is lack of detailed data about the progress of genetic counseling and cascade family screening. Cascade screening is explicitly a part of the Geisinger process, to its credit,[14] though it receives only a token mention about "availability of genetic counseling" in the direct-to-consumer setting. Geisinger has an active program to study the challenges and opportunities of familial cascade genetic counseling for mutations in 76 medically actionable genes, but it will take time to publish even preliminary findings of this inherently time-consuming process.[15]

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If each mutation is akin to a mustard seed, how many can be planted before the plants become an unmanageable forest that could do a lot of damage to the health care ecosystem? At some point, a critical mass of seeds will disperse such that they will become a ubiquitous feature of the global medical ecosystem. However, if everyone were to have a fully sequenced genome in the context of a networked global precision medicine system, then cascade screening of pedigrees would become unnecessary. The problem of notifying and testing family members would be essentially solved if and when everyone, everywhere were to have access to genome sequencing, but it does not seem that this will come to pass anytime soon, if ever. Even if sequencing capacity becomes adequate, the workforce is lacking. There are approximately 3,000 genetic counselors in the United States,[16] and these are already in high demand for traditional clinical genetic practice, especially given the revolution in diagnostic genetic testing that has occurred in the wake of the Human Genome Project.

Social media technology linking family members, their medical records, and mutations might provide a partial solution to the problem, and there is great innovation in process.[17] However, many people will not embrace such matrixed family connectivity, and how can extremely sensitive information, such as a mutation conferring hereditary breast and ovarian cancer susceptibility, ever be communicated tactfully and humanely via social media? Bad news must be delivered with the utmost empathy in medicine. A diagnosis of genetic susceptibility to a severe disease should ideally be disclosed only in an appropriate clinical setting by an empathetic professional.

Another important genetic counseling issue is the informed consent of the patient and relatives. The typical practice in genetic testing of an individual with a known or suspected genetic disorder, whether in the clinical or research setting, is to notify the patient that close relatives may need counseling and possibly testing if a deleterious mutation is detected in the patient. An advisory to discuss with relatives before proceeding with testing is standard. However, when there is a compelling clinical indication for genetic testing, it is rare that a close relative would object to such testing.

In contrast, when a healthy individual wants to undergo experimental genomic screening, the need to do it is not so compelling, yet the bland disclaimer to "discuss with relatives" is the same. The onus is placed squarely on the patient to lead the family discussion, if one ever occurs. If such a discussion doesn't occur, then relatives are denied the opportunity to consent to or decline placement by proxy into an "at-risk risk for familial mutation" category. Even if they decline to know what the mutation is or to be tested, just as a bell can't be unrung, the unconsented relative can't "unknow" their familial risk status.

In "The Love Song of J. Alfred Prufrock," T.S. Eliot alluded to mysterious hands "that lift and drop a question on your plate." It is worth considering, in the context of experimental genomic screening, whether the hands of researchers and clinicians should drop such portentous questions on the plates of patients' relatives. Even if the individual's liberty interest in genomic screening outweighs the relative's interest in providing prior input, researchers and clinicians could be more helpful in facilitating family discussions, perhaps using video aids as in the EMERGE Project, for example.[18]

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The Clinical Validity Gap

"Before you tell 'the truth' to the patient, be sure you know 'the truth' and that the patient wants to hear it." – Attributed to Dr. Richard Clarke Cabot (1868-1939)[19]

Truth is hard to know and to communicate, but conveying uncertainty clearly is even harder. Uncertainty pervades genomic screening, which is founded upon a "three-legged stool" consisting of analytical validity, clinical validity, and medical actionability. Analytical validity in the context of genomic screening is the extent to which mutations can be diagnosed accurately, and this is the strong suit of genomic sequencing, if done according to high standards.[20] However, there are major gaps in knowledge about genotype-phenotype correlation and mutation penetrance in salient subgroups of patients, which are critical data for clinical validity.[21] Even if clinical validity is established, the medical actionability must also be strong, meaning that existing intervention must be safe and effective at the relevant stage of disease. ACMG chose its list of 59 genes based on the ability to intervene and improve the patient's outcome safely and effectively at an early stage of disease,[22] but all prior experience has been in the biased context of familial not general population screening.

Moreover, there exists no comprehensive, definitive list of mutations in medically actionable loci that should necessarily be reported to patients, even when bioinformatic predictions of mutation pathogenicity are confident. Like any imperfect diagnostic

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test with less than 100% sensitivity and specificity, the interpretation of genetic test results depends on the prevalence of the disease in the subpopulation of patients that is tested, with the lowest predictive value of a positive test always occurring in the healthiest populations, as is the case in newborn screening for inborn errors of metabolism.[23]

In addition, individual patient characteristics and circumstances alter genetic test interpretation. A particular genetic mutation found in a newborn may prompt serious concern about future disease risk, whereas its detection in a centenarian would be cause for reassurance that it was nonpenetrant. The sex of the patient may modify the risk of disease, and for imprinted genes, even the sex of the parent from whom it was inherited may determine disease risk.[24]

The molecular genetics of Marfan syndrome, an autosomal dominant condition caused by mutations in fibrillin-1 (*FBN1*) illustrate how the clinical validity gap poses major challenges for genomic screening. *FBN1* "presumed deleterious" mutation prevalence in the general population is 1 in 65,[25] whereas Marfan syndrome clinical diagnosis occurs in 1 in 5000 individuals. Existing *FBN1* mutation databases are unreliable.[26] Echocardiography annually until age 45 and screening of first degree relatives of mutation carriers is standard, and Marfan syndrome is so notoriously variable in expressivity that the diagnosis can't reliably be excluded on clinical grounds, especially in young people.[27] Large, population-based, genotype-phenotype databases are needed for each genomic disease to be screened in order to permit accurate estimation of mutation penetrance and disease-prevention potential for public health purposes. Research at Vanderbilt University Medical Center suggests that integration of genotype-phenotype data in an electronic medical record system may improve the positive predictive value of mutations by selecting patients who show clinical signs of a relevant genetic diagnosis.[28]

The Genomic Health-System Effectiveness Gap

Healthy individuals diagnosed with potentially medically actionable mutations lie, as Anya Prince put it,[29] "in the liminal state between health and disease." Health insurance coverage for medical interventions in asymptomatic individuals based on mutations detected by experimental genomic screening is deniable unless the insurer has a written, specific policy assuring such coverage. Like similar projects elsewhere, the pioneering Geisinger GenomeFIRST project is "stress-testing" the insurance coverage system by releasing mutation data to patients, and the knotty issue of denial of payment has already been encountered by at least one patient, the pseudonymous "Dana Atkinson," a Geisinger Medical Center nurse who screened positive for a Long QT syndrome mutation.

Atkinson has three children, and her eldest son tested positive for the mutation and had evidence of QT interval prolongation on a two-week Holter monitor electrocardiographic study. As reported in Genomeweb,[30] "A cardiologist has recommended he begin taking β-blockers to reduce the risk of his heart going haywire. Atkinson also purchased a $2500 automatic external defibrillator to jump-start his heart if it stops. The cost of the device was not covered by her insurance — even with a Long QT diagnosis."

A case like Atkinson's raises enormously complex legal and ethical questions in case of bad outcomes. If insurance coverage is denied and a parent does not purchase an automatic external defibrillator (AED) for a child but sudden death occurs, who would be held legally responsible for the death, if anyone? For an expensive, potentially life-saving intervention for an at-risk child whose family legitimately could not possibly afford to pay, could a private insurer be compelled to pay? Could the institution that conducted the genomic screening be held financially responsible? If not, would government aid to avert possible medical neglect of the child be forthcoming if parents appealed for help?

In contrast to the foregoing external defibrillator case, there has already been a case of inappropriate internal automated defibrillator (IED) placement due to misinterpretation of a mutation incorrectly believed to be associated with Long QT syndrome.[31] Thus, it is clear that errors of commission as well as omission will occur in genomic medicine, and that benefits should not be touted without reference to possibly serious harms.

American law is unclear, variable, and evolving with respect such novel legal scenarios as described above. LawSeq, a project designed to clarify current law and guide the development of future policy and law, is currently underway,[32] but Atkinson's case highlights the profound unreadiness of health systems, legal systems, and society to answer pressing questions posed by genomic screening. In addition, as health systems look to cut costs while simultaneously increasing quality, there may be little tolerance for genomic screening efforts outside of the research setting. Preliminary evidence from the MedSeq Project suggests that whole genome sequencing of healthy adult patients drawn from the primary care setting so far does not appear to be a clearly cost-effective intervention,[33] so it is likely that there will be ongoing debate and financial resistance to genomic screening within health systems.

Filling the Critical Gaps in Genomic Screening

Proposal of detailed solutions is beyond the scope of the present paper, and must necessarily involve multilateral discussions including all the various stakeholders. In brief, however, I would propose the following solutions to the implementation problems of genomic screening, whether in the direct-to-consumer, clinical care, or research setting. All parties involved in genomic screening should: (1) Limit the scale, scope, and pace of genomic screening until more empirical data are available to guide policy, and so that too many mutations aren't released too quickly into unprepared health systems; (2) Warn that screening of individuals

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without known or suspected genetic disease currently renders mutation interpretation more uncertain than it is in the context of diagnosis or family-based screening; (3) Warn that health insurers may deny coverage, as not medically necessary, of follow up testing and medical intervention in asymptomatic patients who screen positive for a mutation; (4) Provide more robust pre-screen genetic counseling that vividly illustrates the challenging complexity of cascade mutation screening within families, including real-world scenarios of relatives of various ages and personalities who may under- or over-react to counseling information; (5) Research benefits and harms of cascade mutation screening in families and accelerate publication of results; (6) Request more funding for ethical, legal, and social implications of genomic screening with an emphasis on multidisciplinary innovation and implementation of real-world solutions; (7) Prioritize and fully fund large-scale, genotype-phenotype correlation research to fill gaps in knowledge about mutation penetrance and expressivity; (8) Set voluntary standards and policies to avert a genomic screening crisis that could erode trust and necessitate restrictive laws; (9) Determine what the law is and what it should be in relation to genomic screening at local, national, and international levels; (10) Determine how and when health systems can equitably absorb screened patients with susceptibility mutations and intervene effectively to improve their outcomes.

The point is not to slow down research on potentially life-saving genomic screening protocols but to speed up the neglected aspects of family cascade screening, provision of precise genotypic penetrance estimates for clinically relevant subgroups of patients, and crafting of health law and policy to accommodate the projected influx of millions of mutation-positive patients. Genomic precision medicine should be implemented precisely, and it should take its time to fill critical gaps before getting too far ahead of itself. Powerful technology such as Next Generation sequencing should not prompt a "manifest destiny" attitude towards scientific advancement to the exclusion of other societal values.[34] Those who are painstakingly researching the risks and benefits of genomic screening in the context of comprehensive research projects are on the right road. As Muin Khoury of the U.S. Centers for Disease Control has written,[35] there are "no shortcuts on the long road to evidence-based genomic medicine."

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