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We screen newborns, don't we?: realizing the promise of public health genomics

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Genomics and public health have been uneasy bedfellows for some time. Most efforts to improve population health through genomic approaches have focused on the assessment of risks for common diseases, with the aim of tailoring interventions and screening.[1] However, the improvement of population health through such an approach has remained elusive.[2] Now, rapid progress in affordable, robust DNA sequencing offers a promising opportunity. By expanding the field's focus from common to rare diseases, it may be possible to realize the promise of public health genomics by identifying those millions of individuals who unknowingly carry mutations that confer a dramatic predisposition to preventable diseases.

In seeking to apply genomic technologies to public health, the traditional focus on common diseases is understandable. After all, even minor progress in risk reduction for diseases that affect millions of people could have a large beneficial impact. In addition, although potential for this approach certainly remains, we have little to show in terms of improved health after more than a decade of such focus. There may be several reasons for a lack of robust progress on this front. First and foremost, genetics constitutes a relatively small etiologic component of common diseases,[3] a fact that places an inherent ceiling on the utility of genetic risk assessment. Although the possibility exists that more of the risk for common diseases may be explained by gene–exposure interactions, this hypothesis has yet to be realized. Moreover, common diseases are . . . well, common. Thus, the absolute risk for any individual to develop these diseases will remain substantial regardless of our ability to tweak an individual's relative risk by genetic analysis. Therefore, the population at large will likely benefit from public health interventions designed to lower that risk, regardless of their precisely quantified relative risk. Further undermining the utility of modestly adjusting one's risk for common diseases through genomic analysis is the fact that the medical and population prevention tools at our disposal by which to intervene and lower disease risks are blunt, and their use incurs a variety of risks. Experiences with side effects of statins and estrogen replacement therapy for people with modest disease risks show the potential downsides of medical interventions to alter population health risks;[4] medical interventions are usually most beneficial when identified disease risks and potential benefits are high. Finally, efforts that aim for genomic risk stratification often are justified by the hope that simply informing individuals of their genetic risks for disease will induce beneficial behavioral changes.[5] Thus far, this notion is largely contradicted by available evidence.[5,6] Although we already know how to lower risks for most common diseases, getting populations to eat properly, exercise, and give up unhealthy behaviors, especially without major policy changes, is challenging, and there is little evidence to suggest that genetic tweaking of risk will meaningfully augment these efforts.[7,8]

However, recent advances in sequencing technology provide a new opportunity to expand the focus of public health genomics in a way in which its promise can be realized. Millions of people in the United States unknowingly carry (individually rare) mutations that confer dramatic predisposition to preventable diseases. These individuals could readily benefit from existing, validated preventive modalities if knowledge of their underlying genomic risk was available. A case in point is Lynch syndrome. The roughly 0.2% of individuals[9] in the US who harbor deleterious mutations in any one of four Lynch-associated genes are at >80% risk for colon cancer.[10,11] If their high-risk status is known, validated preventive strategies can dramatically reduce their risk of ever developing cancer.[11,12] A number of other genes in the human genome confer very high risk of preventable diseases when mutated, and an aggregate population prevalence of mutations in such genes ranges between 0.5% and 1%. An added benefit of focusing on rare diseases in this manner is that, because of the genetic nature of these disorders, for each at-risk person identified, several other family members are identified who will benefit, thereby amplifying its utility several fold.[13] Although the morbidity and mortality that result from carrying such mutations often is preventable, until now the only way of identifying these individuals has been to wait until they or many of their family members develop life-threatening diseases. It is now feasible to consider identifying such individuals through the broad application of rapid and inexpensive sequencing of targeted genes.

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At first blush, the notion of deriving public health benefit from a focus on rare diseases seems counterintuitive. Indeed, early detection and management of the relatively rare individuals with monogenic risks to develop diseases such as cancer will have a negligible effect on overall cancer mortality. However, if aggregate incidence of disease, practicality of detecting high risk, and ability to intervene are all sufficiently high, identifying such individuals produces profound dividends for many people and their family members. Take the example of newborn screening for disorders such as phenylketonuria. The disorders for which we routinely employ newborn screening are uniformly rare. Nevertheless, by judiciously applying screening to those disorders for which a specific combination of features pertain (serious outcome, effective prevention, asymptomatic latent period, and an affordable assay), it has become an exemplar of successful public health intervention.[14] Now is the time to investigate the potential of applying genomic analysis in adults in a way similar to that which has made newborn screening so successful in the neonatal population.

We urge here that a new partnership be forged between the genomics and public health communities. The partnership would expand the focus from solely common diseases and embrace the newly developed power of genomics to identify those rare (but, in aggregate, substantial number of) individuals in the population who carry highly penetrant mutations that confer a high risk of preventable diseases. This effort would use affordable, massively parallel sequencing technology to sequence a small, defined set of genes that meet the twin bars of high penetrance (high risk of disease when mutated) and effective presymptomatic intervention. A number of candidate loci could be selected for an initial trial of such an approach. Certainly, the major genes associated with Lynch syndrome (*MSH2, MLH1*, and *MSH6*) and certain other highly penetrant cancer predisposition genes (e.g., *APC*, *BRCA1, BRCA2, MYH, PTEN*, and *VHL*) are promising candidates, as are genes associated with high risk for preventable vascular catastrophe (e.g., *FBN1, COL3A1*, and *MYH11*) and possibly familial hypercholesterolemia.

The cost of massively parallel sequencing has declined so dramatically that current estimates for sequencing roughly a dozen such genes in a highly multiplexed fashion from saliva samples would be ~$200 per sample, a number that is likely to decline further in the near future. One must be cautious in making claims of cost savings through the application of new medical technology, but treating diseases that could be prevented is certainly expensive, and it is possible that a well-designed effort to identify and prevent them could prove cost effective, especially if a risk-stratification strategy were used.

Of course, many barriers and challenges must be overcome to implement such a program successfully, especially on a large scale. The selection of the genes to be screened should focus initially on those that have the highest penetrance and are associated with the most effective and acceptable preventive modalities. Minimizing false positives (with a corresponding sacrifice of some degree of sensitivity) is necessary, in part because no confirmatory testing is currently available by which to adjudicate most variants of unknown significance that are inevitably generated upon DNA sequencing. This reality necessitates that the informatic analysis of potential mutations select only clearly deleterious mutations (e.g., those that result in truncation of translation and those already confirmed as deleterious). Such informatic approaches exist and currently are being applied in the analysis of whole-exome sequencing in a clinical context.[15]

In addition to technical challenges, a number of important ethical, legal, and social implications of such a vision must be addressed. Discovery of a highly predisposing mutation is not a diagnosis *per se*, but has the potential to produce anxiety and worry in individuals identified with highly predisposing mutation. However, this is little different from accepted public health screening tests, which also focus on future risks, such as the measurement of cholesterol, blood pressure, or cervical dysplasia. Attempts to assess the feasibility and impact of this general approach should focus on those genes that offer the highest level of potential beneficial impact with the lowest potential for distress and other adverse events. Ultimate determination of which genes and which specific populations would be most promising for such screening should be guided by a process in which candidates are evaluated in a transparent manner by experts and diverse stakeholders. Again, we can learn from the newborn screening community, which has developed a defined process by which diseases that are candidates for inclusion into newborn screening panels are adjudicated based on available evidence and perceptions by stakeholders, including patients and the public.[16] The determination of appropriate population groups, recruitment, assessment, and development of behavioral and community approaches to evaluation and intervention are critical to this line of research. The population perspective and disciplines of public health—epidemiology, health policy, biostatistics, and health behavior—have a critical role in this arena.

Other, ultimately complementary models for applying genomic analysis in a public health context can be envisioned. For example, analysis of conventional risk polymorphisms might eventually allow identification of those who carry a high enough burden of risk variants to indicate targeted preventive measures.[17] However, at present, our ability to calculate meaningful and consistent risk estimates through analysis of common polymorphisms is problematic,[18] making a focus on rarer but more clearly interpretable findings potentially preferable. Likewise, some groups have called for widespread whole-genome sequencing of the general population.[19] However, putting aside the substantial cost, analytic demands, interpretation dilemmas, and informatics requirements of widespread whole-genome sequencing, serious ethical, legal, and social implications quickly arise when contemplating its use at the population level,[20] especially in vulnerable populations. We therefore propose that targeting specifically selected genes is more likely, at least for the present, to realize the promise of genomics in the service of public health.

It remains to be determined whether the application of genomic analysis in the general population as outlined here

would be an effective public health strategy. Many questions must be addressed that will require the expertise of diverse specialties. But the time is ripe for the fields of genomics and public health to join forces and broaden their focus to investigate whether the identification of rare but highly actionable mutations may help realize the promise of public health genomics.

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DISCLOSURE

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