Anticipating the arrival of low-penetrance genetic testing to primary care medicine

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Abstract Primary prevention is a pillar of primary care medicine. Furthermore, the identification of commonly occurring genetic mutations that confer only modest increases in disease risk (i.e., low-penetrance mutations or LPMs) is expanding our conception of how genetic testing supports prevention goals. To date, most predictive genetic testing has focused on identifying the minority of patients who carry mutations that significantly increase their risk for developing future disease (i.e., high-penetrance mutations or HPMs). Genetic tests for LPMs are more similar in structure and purpose to commonly used biomarker tests like lipid testing than to HPM testing. In the primary care setting, LPM testing will likely be presented to patients as one part of a multifactorial risk assessment that contains only a small amount of genetics-specific information. Consequently, preparing primary care clinicians for the anticipated use of LPM genetic tests will not require development of a completely new skill set but

rather a re-conceptualization of both genetic testing and biomarker evaluation for primary prevention.

Abbreviations

HPM	High-penetrance mutations
LPM	Low-penetrance mutations
RR	Relative risk
AR	Absolute risk

Disease prevention is a core mission of primary medical care and generally falls into two categories: primary and secondary preventions. Primary prevention (e.g., lipid testing for cardiovascular disease prevention) aims to prevent disease onset, while secondary prevention (e.g., mammography for breast cancer detection) aims to identify incipient disease before it has produced clinical symptoms. While primary prevention is often referred to as screening, it technically represents risk stratification for primary prevention purposes. The goal of lipid testing is not to detect early atherosclerotic disease but rather to measure a biomarker, the level of which is used to estimate an individual's risk for clinical disease.

Predictive genetic testing (e.g., testing of asymptomatic patients for genetic variants that place them at greater risk for future disease) is an example of primary prevention risk stratification that is likely to assume a more prominent role in the twenty first century primary care practice. To date, scientists have identified numerous mutations associated with common diseases (e.g., hypertension) (Levy et al. 2009) that modestly increase an individual's future disease risk (i.e., low-penetrance mutations or LPMs). Our goal in this paper is to consider, in a conceptual manner, how LPM predictive genetic testing compares to both biomarker testing and other types of genetic testing and also to envision the impact of LPM testing on the primary care practice of clinical risk stratification.

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Testing for low-penetrance mutations

LPMs are fairly prevalent. Therefore, testing for them alongside a family history assessment in a primary care setting is not a novel concept (Burke 2004; Holtzman and Marteau 2000) and may help healthcare providers identify individuals who are at risk for common diseases and might benefit from specific interventions or tailored screening regimens. While LPM testing panels may have multiple clinical uses, in this paper, we are referring to the anticipated use of such testing for primary preventive management for specific diseases in the clinical arena rather than testing for LPMs across multiple diseases (e.g., multiplex genetic testing through DTC companies). Admittedly, LPM testing may not be useful for every disease and, in some instances, may be infeasible due to large numbers needed to screen (Vineis et al. 2001). Nonetheless, we postulate that there will be cases in which LPM testing will offer practical, important information to the primary care clinician who will be responsible for ordering/discussing them.

We acknowledge that such disease-specific LPM testing panels do not currently exist and that identifying clinically significant and valid mutations will be challenging (Geneletti et al. 2011). However, given that current research is devoted to identifying low-penetrance genetic mutations (LPMs), developing inexpensive tests, and assessing clinical utility (Burke and Psaty 2007; Collins et al. 2003), we believe these panels are likely to become available to clinicians in the foreseeable future. Our goal in this paper is to begin a conceptual dialogue about the potential future utilization of LPM panels in primary care medicine.

Similarities between LPM testing and biomarker testing: intersection of genetic testing and primary care

While tests for LPMs are technically “genetic” because they are DNA based, LPM tests actually have more characteristics in common with biomarker tests like the lipid profile than with other types of genetic tests (Table 1).

First, like the lipid profile that identifies modest elevations of relative (RR) and absolute risks (AR) for cardiovascular disease by assessing multiple biomarkers (D’Agostino et al. 2008), LPM panels will test for multiple genetic variants for a specific disease (Kury et al. 2008; Meigs 2009). With both biomarker testing and LPM test panels, the combined prevalence of biomarkers/mutations is higher than individual prevalence (Meigs 2009), which may be rare. While a single LPM may not be clinically significant, an LPM panel enables identification of multiple mutations in higher risk individuals (Yang et al. 2003). In addition, because most common diseases are influenced by multiple

behavioral, environmental, and genetic components, LPM panels may yield changes in RR and AR similar to those seen for tests for biomarker testing. Similar to cardiovascular risk score, data from LPM panels will likely be combined with other clinical characteristics (i.e., age, sex, phenotypic factors) to produce a composite disease risk score.

Second, LPM tests and biomarker tests have similar implications for the patient’s health-related activities and risk perception (Table 1, second section). For most biomarker tests, at-risk individuals are offered preventive interventions that include some combination of lifestyle modification and/or pharmacologic therapy. Such interventions—considered routine, non-urgent, and minimal risk (Expert Panel on Detection 2001)—may alter an individual’s lifestyle but generally do not transform a person’s life or self-identity, as often occurs with HPM testing. For example, an LPM testing panel for colon cancer screening might lead to diet changes or more frequent screening regimens but is unlikely to lead to invasive or aggressive interventions (Manolio et al. 2008).

Third, LPM tests will likely borrow heavily from the procedural model for biomarker testing in which the primary care clinician routinely orders tests because patients meet certain clinical criteria (e.g., age, family history) and the testing will inform clinical care. Ensuing discussions about results are generally brief and communicated only in the context of clinical recommendations and need for further testing. In these situations, the primary care clinician will be responsible for explaining LPM test results to patients without a genetic specialist and within the constraints of their typical 15-min appointment. Genetic-specific language such as “carrier” and “mutation” may be replaced with the “high risk” and “risk factor” language commonly used in discussions with patients about hyperlipidemia and other common chronic conditions.

Clarifying differences: genetic testing for high-penetrance mutations

Until recently, much genetic testing has been limited in scope—conducted almost exclusively by genetic specialists on symptomatic patients with rare Mendelian disorders with complete or near complete penetrance. Advances in genetic testing technologies over the past decade have expanded the testing world of genetics specialists to include predictive genetic testing of asymptomatic individuals for rare mutations with high but not complete penetrance (i.e., high-penetrance mutations or HPMs) (Table 1).

Compared to an LPM or biomarker test result, “positive” HPM test results convey a qualitatively higher risk profile. As a result, they precipitate serious conversations and decisions about interventions and family disclosure (King et al.

Table 1 Comparison of test characteristics: clinical screening, LPM, HPM

	Clinical screening tests	Low-penetrance mutations (LPMs)	High-penetrance mutations (HPMs)
Examples	Lipid profile	Colorectal cancer panel, diabetes panel	BRCA, APOE4
Impact of positive mutations on disease risk	Relative risk change: $\times 1$ – $\times 2$ absolute risk change (generally $<10\%$)	Relative risk change: $\times 1$ – $\times 4$ absolute risk change (generally $<10\%$)	Relative risk change: $\times 4$ – $\times 10$ absolute risk change (10–100 %)
Prevalence of mutations/abnormal test results in general population	Common	Rare individually, more common in aggregate	Rare
Interaction with environment	High	High	Low
Interaction with (other) genes	Common	Common	Rare
Number of genes/biomarkers tested	Varies	Many (all predict same outcome)	Few (often only 1)
Possible interventions if positive for mutations/elevated result	Preventive regimens (diet/exercise)	More frequent cancer screening, preventive regimens (diet/exercise)	More frequent cancer screening, preventive regimens (diet/exercise), chemoprevention, prophylactic surgery
Risk of interventions	Generally minimal	Minimal	Varies from minimal to very high
Possible effects on risk of other conditions	Common	Common, but low impact if found	Rare, but significant if found
Who orders test	Physician-driven and ordered (generally in primary care)	Physician-driven and ordered (generally in primary care)	Patient-initiated (upon clinician recommendation), implemented by genetic specialist
Who discusses test results	By physician, in the context of making a specific clinical decision	By physician, in the context of making a specific clinical decision	By genetic specialist (genetic counselor and/or specialty physician), in the context of personal understanding of future disease risk

2001; Rebbeck et al. 2004; Tercyak et al. 2007) HPM tests therefore involve a significantly different care delivery model with pre-visit preparation and within-visit communication procedures to which primary care clinicians are neither accustomed nor for which they have the time. This resource intensive care delivery model includes a thorough investigation of the patient's family history, medical history and a preliminary risk assessment (Guttmacher et al. 2001). The genetic counseling provided is time intensive, usually requiring an extended (i.e., 60–90 min) appointment (Guttmacher et al. 2001). This model also emphasizes providing support for the emotional effects of testing (Mikkelsen et al. 2009) because HPM test results often have significant impact on self-identity and future medical decision making (Watson et al. 2004). Given the expertise and resources required for this care delivery model, PCPs will be unlikely to conduct HPM testing under this current model and will either refer patients to specialists or provide care in collaboration with those providers with specialized training and experience (Guttmacher et al. 2001).

It is possible that rare HPMs that are associated with common diseases will be identified and included on a testing panel that consists largely of LPMs. However, the probability that a given patient has a rare HPM for a common disease is low, and hence, this concern is unlikely to prevent a PCP from ordering

the test. On rare occasions when an HPM for a common disease is identified, it is likely to trigger management consistent with that for an HPM for a rare disorder.

Communicating about LPM testing in primary care

LPM tests are coming, and it is important to define models for the use and communication of LPM test results prior to their introduction, not afterward. The conceptual argument outlined above suggests that the structure and use of LPM testing will be similar to those of biomarker tests commonly employed in primary care. Therefore, we believe that it is important to shift the focus of discussions about these tests from the testing method used to gather information (e.g., DNA based) to the implications that such testing has for clinical management and discussions of heredity. We include mention of heredity because it is common to both biomarker and LPM testing. For example, discussions of both lipid and LPM testing to predict cardiovascular disease will engender a discussion of family history and inheritance because both conditions have genetic components. However, because LPM testing mirrors biomarker testing in the ways noted above, we believe that it too will be primarily conducted for risk management, not personal genetic exploration. As a result, we believe that when

discussing LPM tests with their patients, clinicians will find it more helpful to draw upon their existing risk communication strategies associated with biomarker testing—strategies which involve explaining the multifactorial nature of disease—than to attempt to apply the methods used in genetic counseling for HPMs.

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