

EXERCISE CAUTION WHEN ORDERING GENETIC TESTS

QUALITY OF EVIDENCE: HIGH ⊕ ⊕ ⊕ ⊕

Why is this important?

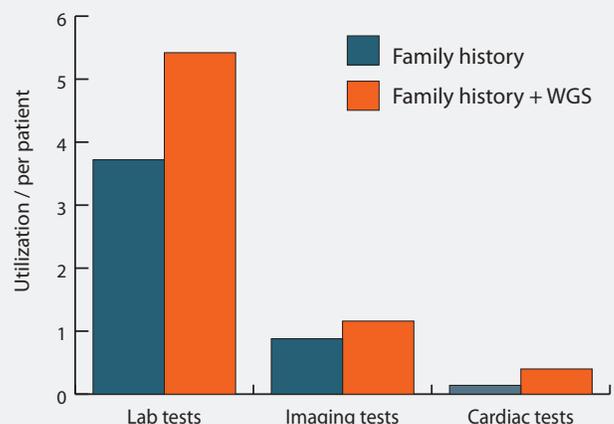
Although genetic testing for germline mutations has been in clinical use for many years, recent advances in sequencing technology allow primary care physicians to order the whole-genome (“next generation”) sequencing of individual patients. In contrast to focused genetic testing, whole-genome sequencing looks for genetic abnormalities across the patient’s entire genome. Unfortunately, there are few guidelines that address the appropriate ordering and use of genetic testing, including whole-genome sequencing, in primary care. Inappropriate testing can lead to patient confusion, incorrect treatments, unnecessary costs, and patient harm.

Facts

- Testing for specific genetic abnormalities has been used for disease prevention, determining diagnoses, informing clinical management, assessing reproductive options, and assisting in life planning.¹ Genetic testing is underutilized in some appropriate situations, such as tumor mutation testing, and overutilized in most other situations.² One study in an obstetrics-gynecology clinic showed that 21% of the genetic tests were not indicated, results from 10.5% of the tests were inadequate for informing clinical decision making, and 7% of the tests provided false reassurance to the clinicians and patients.³
- Primary care testing for specific genes related to drug metabolism has given rise to the burgeoning field of pharmacogenomics.⁴ Currently, there are genetic tests (mostly of cytochrome P450 genes) that assess a patient’s metabolism for over 140 drugs – but it is not clear that they improve clinical outcomes.⁴
- In terms of patient information, only half of breast cancer patients who received genetic testing discussed the results with a genetic counselor⁵⁻⁷ and it has been recommended that Internists work closely with genetic counselors in identifying patients who should receive genetic testing.⁸

- The National Institutes of Health Genetic Testing Registry primarily consists of genome-wide association studies. It contains 52,601 tests for 16,236 genes and common variants which claim to provide information about 10,824 medical conditions.⁹ Unfortunately, it is difficult to establish quantitative risk estimates for many of these genes and common variants.¹⁰ Furthermore, there is a 15% - 26% discordance rate in the pathogenic classification of variants in hereditary cancer genetic testing.¹¹
- Whole-genome sequencing reports include information regarding monogenic disease risk (associated with Mendelian disorders), carrier variants, pharmacogenomic associations, and polygenic risk estimates for cardiometabolic traits.¹²
- The availability of whole-genome sequencing, when added to family history, has led to an increase in the genetic testing of asymptomatic adults in the primary care clinic¹⁰ (Figure), but whole-genome sequencing possesses uncertain clinical utility and value.¹² Its high false positive rate and indistinct relationship to disease suggest that they may cause more harm than good. For example, its results can instigate the ordering of tests to rule in or out diseases when, in fact, the diseases are extremely unlikely to be present in the patient.¹²

Comparison of family history vs. family history + whole-genome sequencing in the ordering of additional tests in asymptomatic patients in a primary care clinic¹⁰



THE BOTTOM LINE

Genetic tests are incorrectly ordered in approximately one-third of the patients,³ their clinical utility in many situations has not been established,^{10,11} and even when a genetic test has been shown to be appropriately ordered and clinically useful, interpreting the test results can be difficult and may require the assistance of genetic counselors.^{5-8,13}

Quality of Evidence

(Adapted from Guyatt G BMJ, 26 April 2008)

This refers to the degree to which the findings of this study are likely to be free of bias.

⊕ ⊕ ⊕ ⊕	High
⊕ ⊕ ⊕ ○	Moderate
⊕ ⊕ ○ ○	Low
⊕ ○ ○ ○	Very low

Tips for Discussion of Results with Patients

- It is only appropriate to order a genetic test if it has been shown to be reliable and clinically useful, i.e., if it will change patient management, for a specific medical indication. One example is the use of BRCA testing in breast cancer.
- Ordering genetic testing without a specific indication, given its high false positive rate and its indistinct relationship to disease, is usually not clinically useful.
- Before ordering any genetic test, the clinician should discuss with the patient the benefits and risks related to the test.¹³
- The clinician should recognize that explaining the results of genetic tests to patients can be complex and require specialized expertise.¹³

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Written by the Evidence-Based Medicine Task Force

Jamie A. Jarmul, PhD
Harry B. Burke, MD, PhD
Zackary Berger, MD, PhD
Michael E. Bowen, MD, MPH, MSCS
Jocelyn Carter, MD

Bill Fuller, MD
Devan Kansagara, MD
Bill Kormos, MD
Edward Murphy, MD
Rani Nandiwanda, MD

Monica Peek, MD
Jeff Tice, MD
Stephanie Wheeler, MD, MPH
Clark Veet, MD



The Bottom Line summaries reflect the expertise and opinions of the SGIM EBM Task Force as of the date of release of this summary. For additional information contact: Harry B. Burke, MD, PhD, harry.burke@usuhs.edu