

CLINICAL DECISIONS

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Screening an Asymptomatic Person for Genetic Risk

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

Jim Mathis is a 45-year-old health-conscious man who has been a patient in an internal medicine–primary care practice for several years. At today’s visit, he talks about the family tree that he has sketched out and his discovery that three of his relatives had cancer — one had breast cancer, one ovarian cancer, and one prostate cancer.

Normally, Mr. Mathis is not an anxious patient, but he does pay close attention to his health. He exercises regularly and runs in half-marathons with his wife during family weekends. He pays attention to his diet, understands many medical terms, and knows the results of his most recent laboratory tests. He sees his physician twice a year for a physical examination and for adjustment of his medication for exercised-induced asthma. The medications include an inhaler before exercise and an oral prophylactic medication. He has no allergies. He was admitted to the hospital once last year for an exacerbation of asthma. In the past, the only conditions he has mentioned in his family history are hypertension and stroke.

During the visit today, his family history is

reviewed. Mr. Mathis tells you that the family tree was constructed at a genealogy workshop that he attended after visiting cousins in Europe. During a discussion of the family tree with his 70-year-old mother, he learned that his aunt had died of breast cancer when she was 52 years of age and that his uncle had had fatal prostate cancer. Another female relative had had ovarian cancer, but his mother couldn’t recall which relative had that cancer or what the outcome was. He says that he has read about whole-genome sequencing, which he defines as the determination of the DNA sequence of all a person’s genetic material.

He asks about genetic testing and about any preventive measures he can take “before the cancer gets me.” You tell Mr. Mathis that genetic screening can be performed to identify genetic susceptibility to cancer, with the use of panels of cancer genes, or to identify genetic susceptibility to genetic diseases as well as cancer, which would involve whole-genome sequencing.

Do you think that Mr. Mathis should undergo genetic screening? If so, should he be referred for

Glossary

Exon: The portion of a gene that encodes amino acids.

Gene panel: A gene panel is designed to evaluate coding and certain noncoding parts of genes that, when mutated, are known to cause a specific disease or confer a risk for that disease. Cancer gene panels typically include more than 100 genes, including oncogenes and tumor-suppressor genes (mutations in which can confer susceptibility to a heritable cancer syndrome). Gene panels can also be used to evaluate tumor tissue for prognostic or therapeutic uses.

Intron: The portion of a gene that is transcribed to messenger RNA (mRNA) but then removed (spliced out) before translation of the mRNA to a protein. Introns may contain regulatory information that is critical to appropriate gene expression, and intron mutations can be pathogenic.

Variant: A difference in a DNA sequence as compared with the normal reference. A variant may be benign (sometimes referred to as a polymorphism) or pathogenic (sometimes referred to as a mutation).

Whole-exome sequencing: Sequencing of the coding regions, or exons, of an entire genome.

Whole-genome sequencing: DNA sequencing that targets the entire genome, even though coverage is not 100%; sometimes termed genome shotgun sequencing. Whole-genome sequencing provides the sequence of coding regions of DNA (exons) as well as noncoding regions of the genome, including introns and intergenic regions.

whole-genome sequencing or sequencing of cancer genes only? Which of the following options would you recommend for him?

1. Recommend sequencing of cancer genes only, if certain conditions are met.
2. Recommend whole-genome sequencing.

To aid in your decision, two experts in the field defend these approaches in the essays below. On the basis of your reading of published literature and other information sources, your clinical experience, your knowledge of the patient's history, and your assessment of the experts' opinions, which option would you choose? Make your choice and offer your comments at NEJM.org.



Choose an option and comment on your choice at NEJM.org

OPTION 1

Recommend Sequencing of Cancer Genes Only, if Certain Conditions Are Met

Wylie Burke, M.D., Ph.D.

Mr. Mathis's family history of cancer could indicate inherited risk, and genetic testing might help to define his risk. However, more information is needed before testing is performed. Furthermore, if testing is pursued, a whole-genome analysis is not the best approach, nor is this patient the right person to test.

The first step in the decision-making process is obtaining a detailed family history. Were all the relatives with cancer biologically related to the patient? If so, this family history may indicate the hereditary breast-ovarian cancer syndrome, a genetic predisposition caused by mutations in the *BRCA1* and *BRCA2* genes, leading to an increased risk of breast cancer (in both women and men), ovarian cancer, and, to a lesser degree, prostate cancer.¹ Some other genes are associated with an increased risk of breast or ovarian cancer, and although most are either rarer than *BRCA1/2* or associated primarily with other cancers, they should, nevertheless, be considered. Genes associated primarily with the risk of prostate cancer are also known, but their use in guiding care has not been established.

Before testing, it is also important to confirm that all the affected relatives are in the same biologic line. For example, if the aunt with breast cancer was the mother's sister and the aunt with ovarian cancer was the father's sister, their cancers are probably unrelated, and concern about inherited risk would be reduced. If the affected relatives are in the same biologic line, a cancer history should be obtained for other relatives in that line. Genetic counseling

can help this evaluation and guide family members through their testing options.² Living relatives with a history of cancer are most likely to have informative genetic testing results. A review of the family history may also suggest other inherited cancer syndromes. For example, a family history of early-onset brain tumors or osteosarcomas would suggest the Li-Fraumeni syndrome, an inherited cancer syndrome accounting for a small percentage of inherited breast cancers.³

The second step in the decision-making process is identifying the person to be tested. A living biologic relative who has breast or ovarian cancer (for example, a daughter of one of the deceased aunts) would be the best person to test. If the test is positive, identifying a genetic mutation associated with cancer risk, other family members can be tested to determine whether they have inherited that risk. If the test result is normal, there are two possible explanations — either a genetic risk is not, in fact, present in the family or the particular genetic risk in the family has not yet been defined and is therefore not discoverable by testing. In either of these cases, testing of unaffected family members would be uninformative. In the case presented here, if no affected relative is available for testing, the next best person would be Mr. Mathis's mother (assuming that all the affected relatives are on her side of the family) because she is more likely than Mr. Mathis to have inherited the familial risk. If a cancer-predisposing mutation is found, it will inform her health care, and Mr. Mathis can then be tested for it to assess his own risk.

The third step in the decision-making process is determining the best test to perform. Whole-genome sequencing generates a host of extraneous results, some potentially confusing or distracting, and is more costly to interpret. In keeping with the principle of focusing testing on the clinical question, the best testing approaches

would either use a targeted gene sequencing panel, testing comprehensively for mutations in genes known to be associated with inherited breast and prostate cancer risk, or start with *BRCA1/2* testing and proceed to more comprehensive testing if the results are normal.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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OPTION 2

Recommend Whole-Genome Sequencing

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To investigate cancer risk, genomewide genetic testing should be performed on an affected family member, with subsequent testing in at-risk relatives for the specific genetic variant implicated by the genomewide testing of the affected person. However, it is a common situation in clinical genetics that at-risk relatives request testing to evaluate their own risks, and no affected family member is available. Such testing has the potential to provide lifesaving, cancer-preventing treatment⁴ — as shown in the case of actor Angelina Jolie.⁵ It should not be denied to our patients. However, there is much controversy about what form such testing should take. Mr. Mathis should undergo whole-genome sequencing if testing cannot first start with an affected family member.

Whole-genome sequencing costs almost the same as custom cancer-gene sequencing. The choice of test hinges on which test is likely to produce a definitive answer to the clinical question at hand.

Whole-genome sequencing has several important technical advantages over gene-panel sequencing and exome sequencing, which require either polymerase-chain reaction or another method, such as capture, to “enrich” the coding regions of the genome (the exome) before sequencing. A risk of both gene-panel sequencing and exome sequencing is that they may “lose” DNA variants or fail to capture certain regions of the exome, thus compromising sensitivity and

resulting in appreciable false negative rates for genetic changes in the coding regions of cancer genes. In addition, neither of these methods can detect genomic rearrangements (which result, for example, in the shuffling of coding parts of the gene, as is frequently seen in *BRCA1*) or the deletion of whole exons (which occurs, for example, with the breast-cancer susceptibility gene *CHEK2*⁶). Whole-genome sequencing not only is less susceptible to these weaknesses, but also provides sequence of noncoding DNA, including introns. There are five relatively common intronic mutations in *BRCA1* that are missed by exon sequencing.

Another benefit of whole-genome sequencing is the potential for secondary findings — that is, clinically relevant variants in a person that have only tangential relevance to the question at hand, but knowledge of which could prove to be critical to that person’s care. For example, recent guidelines recommend that before 5-fluorouracil therapy is initiated, patients should be screened for variants in genes that affect the response to that drug⁷; if a patient requiring 5-fluorouracil therapy had previously undergone whole-genome sequencing, testing that might delay the initiation of therapy could be avoided. Beyond such common variants, rare genetic risks such as vincristine toxicity associated with variants that cause Charcot-Marie-Tooth disease may also be identified. Knowledge of such variants before chemotherapy is initiated can help to prevent toxic effects of therapy.

Whole-genome sequencing provides a repository of variation across the entire genome, regardless of current knowledge — or lack thereof — of the identity, function, and relevance of a gene to the risk of disease. As new genes are identified that, when mutated, confer a risk for cancer, new risk information can be provided to the person.

Beyond the advantages of whole-genome sequencing in identifying a predisposition to cancer and informing therapeutic choices, whole-genome sequencing has the potential to provide information on the genetic risk of other diseases, such as hemochromatosis or disorders of lipid metabolism. Such results have the potential to improve or refine risk-prevention strategies for the patient. Since the potential benefits of many screening programs are controversial,⁸ the report

of secondary findings is not mandated by most testing laboratories. In situations in which physicians or patients consider the benefits of the report of secondary findings to be outweighed by the potential harms, they can elect not to have those findings reported to them. Consequently, the possible harm associated with secondary findings should not be considered a necessary drawback of whole-genome sequencing.

In conclusion, if an affected relative is not available, whole-genome sequencing offers the best chance of determining whether Mr. Mathis is at risk for heritable cancer. With this testing, he may also choose to find out about any risks associated with cancer treatment or about other genetic health risks that he may have.

Disclosure forms provided by the author are available with the full text of this article at [NEJM.org](http://www.nejm.org).

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