Current prostate cancer genetic testing capabilities and considerations

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With the advent of next-generation sequencing technologies, genetic testing of prostate cancer patients is now typically done using multi-gene panels. These vary from targeted disease-specific panels to comprehensive (pan-cancer) panels, with advantages and disadvantages for each. This paper reviews a number of issues raised in choosing the best panels and labs to use, and issues presented by the increasing availability of direct-to-consumer testing.

Key Words: prostate cancer, genetic testing, gene panels, direct to consumer

Introduction

With the introduction of next-generation sequencing, clinical practice has rapidly moved from testing individual candidate gene(s) to the simultaneous testing of multiple genes on a single panel.[1] While this has decreased costs and accelerated identification of patients with mutations, panel testing raises its own concerns.

Disease-specific versus broader panels

Some panels are disease-specific, testing only for genes known (and/or suspected) to be associated with a given condition such as prostate cancer. The advantages of this are that it reduces the likely of getting a result in a gene that either does not explain the patient's history, or that raises unexpected management issues (e.g., prophylactic surgery) for cancers that weren't previously of concern to the family. The disadvantages are that it may fail to test for syndromes that don't clearly entail prostate cancer risk but do present significant risks for other cancers. It may also fail to identify families with an atypical presentation of a syndrome. For example, Lynch syndrome is classically associated with GI, uterine, ovarian cancers. Recently, however, some evidence has suggested an association with a moderate-risk for prostate cancer as well.[2] Ordering a prostate-specific panel that does not include the Lynch syndrome genes could fail to identify an affected family. Thus using broader panels increases the chance of identifying a hereditary syndrome. However this comes at the risk of an increased likelihood of identifying a variant of uncertain significance, as well as an increased chance of finding a mutation in a gene that does not explain the prostate cancer and/or is not clinically actionable.

Clinically-actionable panels

As a compromise, many labs offer "clinically-actionable" panels whose genes all have established management guidelines (for at least some cancer types) if a mutation is found. These panels may often include genes for cancers other than prostate cancer, however. In addition, the "actionability" of most genes is not clearly established for prostate cancer management, and the benefits may be more for managing the risks of cancers other than of the prostate. A purely clinically-actionable panel might also leave out probable prostate cancer genes without established management guidelines, such as *HOXB13*.

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Available prostate-specific panels

Currently at least six major testing labs offer prostate-specific gene panels (Ambry Genetics, Baylor, Fulgent, GeneDx, Invitae and Prevention Genetics). Of these, all six labs include the *BRCA1* & 2, *CHEK2*, *NBN* and *TP53* genes, and five also include *ATM*, the Lynch syndrome genes and *HOXB13*. Four of these labs also offer *PALB2* and *RAD51D*, and three labs include *BRIP1* and *RAD51C*. One lab offers *ATR*, *FANCA* and *GEN1* as well. Thus a variety of panel options are available even within a small number of labs.

Selecting a laboratory

While there are a number of well-established laboratories in the cancer-genetics field, there are also an increasing number of start-up labs offering services that may appear to match those of established companies. When picking a laboratory, a number of questions should be asked. Among others, these include:

1. Are the lab directors experienced and appropriately trained?
2. Is the lab accredited?
3. What tests does the lab perform (limited or broad spectrum)?
4. Are the appropriate genes included on the panels offered?
5. What testing methodologies are used? What is the depth of coverage (average versus minimum) for their panels? Is Sanger sequencing used to confirm positive results?
6. How robust is their program for classification of variants of uncertain significance? Are providers re-contacted if a variant is reclassified?
7. What are the list prices versus costs to patients?
8. What are the billing and patient financial assistance policies of the lab?

Direct-to-consumer (DTC) testing

To complicate matters, a number of companies now offer DTC testing that includes prostate cancer risks. Although some of these companies offer next-generating sequencing similar to traditional testing, most are offering SNP-based panels that can only indicate a genetic association with prostate cancer risk, rather than identification of an actual causative gene mutation. In addition, most of these do not provide pre- or post-test genetic counseling, so that patients who present to a provider with these results often have little or no understanding of what they mean. Some labs doing association-type studies will provide their raw data to a patient, who can then go to a third party provider to have this data analyzed. Positive results received from this type of testing should always be confirmed in a traditional clinical lab since the rate of false positives is high.[3] Not surprisingly, additional time, effort and expense are required to clarify these situations with patients.

Summary

In summary, providers are faced with an increasingly complex array of genetic testing choices that require careful consideration and navigation. As always, patients need to be fully informed before consenting to prostate cancer genetic testing and at receipt of results.

Disclosures

Dr Robert T. Pilarski has no disclosures. □

References

1. Hall MJ, Forman AD, Pilarski R, Wiesner G, Giri VN. Gene panel testing for inherited cancer risk. *J Nat Compr Canc Netw* 2014;12(9): 1339-1346.
2. Dominquez-Valentin M, Sampson JR, Seppala TT et al. Cancer risks by gene, age and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med* July 24, 2019. Epub ahead of print.
3. Tandy-Connor S, Guiltinan J, Krempely K et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet Med* 2018(12):1515-1521.