traditional genetic testing. As cost declines, WES may be more widely used. Whole-genome sequencing is also commercially available. Although it may be quite feasible to sequence the entire genome, there are many issues in doing so, including the daunting task of analyzing the vast amount of data generated. Other issues include: (1) the optimal way in which to obtain informed consent, (2) interpretation of frequent sequence variation of uncertain significance, (3) interpretation of alterations in genes with unclear relevance to specific human pathology, and (4) management of unexpected but clinically significant genetic findings.

Testing strategies are evolving as a result of these new genetic testing platforms. As the cost of multiple gene panels and WES continue to fall, and as interpretation of such test results improve, there may be a shift from sequential single-gene (or a few genes) testing to multigene testing. For example, presently, a 30-year-old woman with breast cancer but no family history of cancer and no syndromic features would undergo *BRCA1/2* testing. If negative, she would subsequently be offered *TP53* testing. Notably, a reasonable number of individuals offered *TP53* testing for Li-Fraumeni syndrome decline because mutations are associated with extremely high cancer risks (including childhood cancers) in multiple organs and there are no proven interventions to mitigate risk. Without features consistent with Cowden syndrome, the woman would not be routinely offered *PTEN* testing or testing for *CHEK2*, *ATM*, *BRIP*, *BARD*, *NBN*, and *PALB2*. However, it is now possible to synchronously analyze all of the aforementioned genes, for a nominally higher cost than *BRCA1/2* testing alone. Concerns about such panels include appropriate consent strategies related to unexpected findings, VUS, and unclear clinical utility of testing moderate-penetrance genes. Thus, changes from the traditional model of single-gene genetic testing should be done with caution (Fig. 84-2).

Limitations to the accuracy and interpretation of genetic testing exist. In addition to technical errors, genetics tests are sometimes designed to detect only the most common mutations. In addition, genetic testing has evolved over time. For example, it was not possible to obtain commercially available comprehensive large genomic rearrangement testing for *BRCA1* and *BRCA2* until 2006. Therefore, a negative result must be qualified by the possibility that the individual may have a mutation that was not included in the test. In addition, a negative result does not mean that there is not a mutation in some other gene that causes a similar inherited disorder. A negative result, unless there is known mutation in the family, is typically classified as uninformative.

VUS are another limitation to genetic testing. A VUS (also termed *unclassified variant*) is a sequence variation in a gene where the effect of the alteration on the function of the protein is not known. Many of these variants are single nucleotide substitutions (also called missense mutations) that result in a single amino acid change. Although many VUSs will ultimately be reclassified as benign polymorphisms, some will prove to be functionally important. As more genes are sequenced (for example, in a multiplex panel or through WES), the percentage of individuals found to have a VUS increases significantly. The finding of a VUS is difficult for patients and providers alike and complicates decisions regarding medical management.

Clinical utility is an important consideration because genetic testing for susceptibility to chronic diseases is increasingly integrated into the practice of medicine. In some situations, there is clear clinical utility to genetic testing with significant evidence-based changes in medical management decisions based on results. However, in many cases, the discovery of disease-associated genes has outpaced studies that assess how such information should be used in the clinical management of the patient and family. This is particularly true for moderate- and low-penetrance gene mutations. Therefore, predictive genetic testing should be approached with caution and only offered to patients who have been adequately counseled and have provided informed consent.

Predictive genetic testing falls into two distinct categories. Presymptomatic testing applies to diseases where a specific genetic alteration is associated with a near 100% likelihood of developing disease. In contrast, predisposition testing predicts a risk for disease that is less than 100%. For example, presymptomatic testing is available for those at risk for Huntington's disease; whereas, predisposition testing is considered for those at risk for hereditary colon cancer. It is important to note that for the majority of adult-onset disorders, testing is only predictive. Test results cannot reveal with confidence whether, when, or how the disease will manifest itself. For example, not everyone with the apolipoprotein E4 allele will develop Alzheimer's disease, and individuals without this genetic marker can still develop the disorder.

The optimal testing strategy for a family is to initiate testing in an affected family member first. Identification of a mutation can direct the testing of other at-risk family members (whether symptomatic or not). In the absence of additional familial or environmental risk factors, individuals who test negative for the mutation found in the affected family member can be informed that they are at general population risk for that particular disease. Furthermore, they can be reassured that they are not at risk for passing the mutation on to their children. On the other hand, asymptomatic family members who test positive for the known mutation must be informed that they are at increased risk for disease development and for transmitting the alteration to their children.

Pretest counseling and education are important, as is an assessment of the patient's ability to understand and cope with test results. Genetic testing has implications for entire families, and thus individuals interested in pursuing genetic testing must consider how test results might impact their relationships with relatives, partners, spouses, and children. In families with a known genetic mutation, those who test positive must consider the impact of their carrier

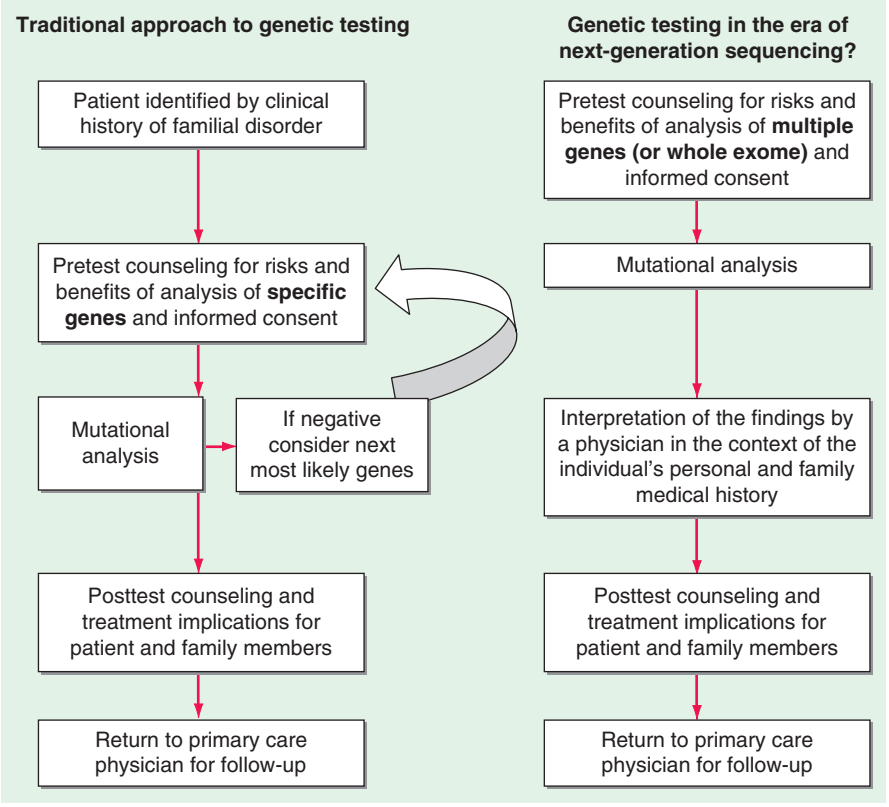

FIGURE 84-2 Approach to genetic testing.