# Gene Panel Testing for Inherited Cancer Risk

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**Abstract**

Next-generation sequencing technologies have ushered in the capability to assess multiple genes in parallel for genetic alterations that may contribute to inherited risk for cancers in families. Thus, gene panel testing is now an option in the setting of genetic counseling and testing for cancer risk. This article describes the many gene panel testing options clinically available to assess inherited cancer susceptibility, the potential advantages and challenges associated with various types of panels, clinical scenarios in which gene panels may be particularly useful in cancer risk assessment, and testing and counseling considerations. Given the potential issues for patients and their families, gene panel testing for inherited cancer risk is recommended to be offered in conjunction or consultation with an experienced cancer genetic specialist, such as a certified genetic counselor or geneticist, as an integral part of the testing process. (*J Natl Compr Canc Netw* 2014;12:1339–1346)

Next-generation sequencing (NGS) technologies have ushered in a new era of genetic testing with the capability of sequencing multiple genes at a single time.[1,2] The overall approach of NGS involves shearing and immobilizing DNA template molecules, usually on a solid surface, for simultaneous sequencing reactions (typically millions to billions) to be performed in parallel.[3,4] *Gene panel testing* refers to sequencing multiple prespecified genes using NGS sequencing platforms. Testing can be performed in the context of assessing for mutations in the germline related to inherited cancer risk, or testing for genetic mutations in a solid tumor or leukemia/lymphoma to gain insights into somatic mutations involved in carcinogenesis and potentially inform targets for treatment.[2] Recently, gene panel tests (or multigene panels) using NGS technology have been introduced by several commercial genetic testing laboratories and academic institutions. This article provides an overview of gene panel testing for inherited cancer risk assessment and highlights the potential benefits and emerging challenges of this novel approach to genetic testing.

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## Gene Panel Testing

Genetic testing options for cancer risk assessment continue to grow in complexity and variety. As of April 2014, at least 7 clinical laboratories in the United States offer gene panel tests evaluating hereditary cancer risk genes. Panels can include genes of high or moderate penetrance. *High-penetrance genes* are those in which mutations confer a high lifetime risk for manifesting the predicted phenotype, usually ranging from 70% to 100%. Examples of high-penetrance genes include *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *STK11*, *PTEN*, *TP53*, and *APC*. *Moderate-penetrance genes* are those in which mutations confer a modest lifetime risk ranging from 30% to 60% for the predicted phenotype, with risk of disease manifestation likely influenced by other genetic or environmental modifiers. Examples of moderate-penetrance genes include *CHEK2*, *ATM*, and *PALB2*.[2] Clinicians may now choose from primarily 4 general approaches to genetic testing for inherited cancer susceptibility: (1) syndrome-specific test (eg, *BRCA1* and *BRCA2* for hereditary breast and ovarian cancer),

(2) cancer-specific high-penetrance gene panel, (3) cancer-specific gene panel with high- and moderate-penetrance genes, and (4) "comprehensive" cancer panels that include genes associated with multiple cancers or hereditary cancer syndromes. These tests differ in the number of genes tested and the technology used in interrogating each gene. Table 1 shows examples of gene panel tests available to clinicians for the evaluation of breast cancer risk from 6 clinical laboratories.

### Syndrome-Specific Test

Syndrome-specific testing remains the most straightforward and generally the fastest testing available. For most of these tests, the genes are analyzed using Sanger sequencing and deletion duplication technologies, with results reported within 1 to 2 weeks. The potential for uncertain test results is typically less than that with larger panels because of substantial testing experience, prospective data curation, and variant classification efforts.[5,6] Turnaround time to receive test results may be particularly important to patients using results to guide cancer treatment decisions, such as potential bilateral mastectomy for newly diagnosed breast cancer in a *BRCA1* carrier. Detailed medical management guidelines for patients affected by a specific genetic syndrome are often available through professional societies or consensus guidelines, such as those of NCCN or the American Cancer Society.

### Cancer-Specific, High-Penetrance Gene Panels

Many laboratories have panels that include predominantly actionable genes relevant to a particular cancer with clear associated cancer risks and management guidelines, such as a high-risk breast panel including *BRCA1/2*, *CDH1*, *PTEN*, *STK11*, and *TP53*. A clear benefit to this type of panel is that there is often phenotypic overlap between genes that may be clinically indistinguishable, depending on family structure. Therefore, a panel that includes genes implicated in the phenotype is often the most economical and overall time-saving approach. The ability to offer testing for several genes may be of benefit to both clinicians and patients through reducing efforts to test multiple genes individually, reducing the need for repeated follow-up visits, and improving the ability to detect mutations across a spectrum of relevant genes simultaneously.

### Cancer-Specific Panel With High- and Moderate-Penetrance Genes

Many panels now include high- and moderate-penetrance genes that could also contribute to a specific cancer risk. The addition of moderate-penetrance genes to clinical panels adds a level of complexity regarding interpretation and medical management based on identified mutations in these genes,[7] with uncertainty often stemming from factors such as lack of understanding of penetrance, average age at diagnosis, and tumor spectrum. Most panel variability between commercial laboratories comes from the moderate-penetrance genes included on various panels.

### Comprehensive Cancer Risk Panels

Larger cancer risk panels that include 25 to 49 genes have now emerged that include moderate- and high-penetrance genes that are associated with a wide variety of cancer types, many of which may not be present in the patient/family, and for which genetic testing would not otherwise be considered. A particularly complicated personal or family history, or a suspicion of multiple cancer syndromes, may compel a patient or clinician to order a comprehensive cancer panel. However, with a larger number of genes comes an accompanying greater chance of finding genetic alterations with unclear medical or cancer risk management.

## Potential Advantages and Emerging Challenges of Gene Panel Testing

### Potential Advantages of Gene Panel Testing for Inherited Cancer Risk Assessment

Advantages to a panel testing approach in hereditary cancer risk assessment are many (Table 2). Among the strongest arguments for panel testing is that hereditary cancer syndromes and their associated phenotypes frequently have considerable overlap in presentation and associated malignancies. For example, ovarian cancer is a common manifestation of mutations in both the *BRCA1/2* genes of hereditary breast-ovarian syndrome and the mismatch repair genes of Lynch syndrome. Testing for both syndromes with a multigene panel allows risks for these syndromes to be assessed simultaneously, and for other genes that could contribute to ovarian cancer risk but about which testing and clinical data are still limited. One study identified 63 *BRCA1/2* mutations in patients

**Table 1 Sample Gene Panel Test Options for Assessing Breast Cancer Risk as of July 2014**

| Company/ Laboratory | University of Washington | Myriad Genetics | Ambry Genetics | | | | GeneDX | | Baylor | | Invitae | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Panel Name | BROCA | myRisk | BRCAplus | GYNplus | BreastNext | OvaNext | High-Risk Breast | Breast/ Ovarian | High-Risk Hereditary Breast | Breast/ Ovarian | High-Risk Hereditary Breast | Women's Hereditary Cancers | Custom Panel |
| Total No. of Genes | 49 | 25 | 6 | 9 | 18 | 23 | 6 | 21 | 7 | 23 | 6 | 17 | ≤29 |
| Gene | | | | | | | | | | | | | |
| *AKT1* | x | | | | | | | | | | | | |
| *APC*[a] | x | x | | | | | | | | | | | x |
| *ATM*[b] | x | x | | | x | x | | x | | x | | x | x |
| *ATR*[b] | x | | | | | | | | | | | | |
| *BAP1* | x | | | | | | | | | | | | |
| *BARD1* | x | x | | | x | x | | x | | x | | | |
| *BMPR1A* | x | x | | | | | | | | | | | x |
| *BRCA1*[a] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| *BRCA2*[a,b] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| *BRIP1*[b] | x | x | | | x | x | | x | | x | | x | x |
| *CDH1*[a] | x | x | x | | x | x | x | x | x | x | x | x | x |
| *CDK4* | x | x | | | | | | | | | | | x |
| *CDKN2A* | x | x | | | | | | | | | | | x |
| *CHEK1* | x | | | | | | | | | | | | |
| *CHEK2* | x | x | | | x | x | | x | | x | | x | x |
| *CTNNA1* | x | | | | | | | | | | | | |
| *EPCAM*[a] | x | x | | x | | x | | x | | x | | x | x |
| *FAM175A* | x | | | | | | | | | | | | |
| *FANCC*[b] | | | | | | | | x | | | | | |
| *GALNT12* | x | | | | | | | | | | | | |
| *GEN1* | x | | | | | | | | | | | | |
| *GREM1* | x | | | | | | | | | | | | |
| *HOXB13* | x | | | | | | | | | | | | |
| *MLH1*[a] | x | x | | x | | x | | x | | x | | x | x |
| *MRE11A*[b] | x | | | | x | x | | | | x | | | |
| *MSH2*[a] | x | x | | x | | x | | x | | x | | x | x |
| *MSH6*[a] | x | x | | x | | x | | x | | x | | x | x |
| *MUTYH*[a] | x | x | | | x | x | | | | x | | | x |
| *NBN*[b] | x | x | | | x | x | | x | | x | | x | x |
| *NF1*[b] | | | | | x | x | | | | | | | |
| *PALB2*[b] | x | x | | | x | x | | x | x | x | | x | x |
| *PIK3CA* | x | | | | | | | | | | | | |
| *PMS1* | | | | | | | | | | x | | | |
| *PMS2*[a] | x | x | | x | | x | | x | | x | | x | x |
| *POLD1* | x | | | | | | | | | | | | |
| *POLE* | x | | | | | | | | | | | | |
| *PRSS1* | x | | | | | | | | | | | | |
| *PTEN*[a] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| *RAD50*[b] | x | | | | x | x | | | | x | | | |
| *RAD51* | x | | | | | | | | | | | | |
| *RAD51C*[b] | x | x | | | x | x | | x | | x | | x | x |
| *RAD51D*[b] | x | x | | | x | x | | x | | x | | | |
| *RET*[a] | x | | | | | | | | | | | | x |
| *SDHB* | x | | | | | | | | | | | | |
| *SDHC* | x | | | | | | | | | | | | |
| *SDHD* | x | | | | | | | | | | | | |
| *SMAD4* | x | x | | | | | | | | | | | x |
| *STK11*[a] | x | x | x | | x | x | x | x | x | x | x | x | x |
| *TP53*[a] | x | x | x | x | x | x | x | x | x | x | x | x | x |
| *TP53BP1* | x | | | | | | | | | | | | |
| *VHL*[a] | x | | | | | | | | | | | | x |
| *XRCC2* | x | | | | | | | x | | | | | |

[a]Genes with professional or consensus guidelines for medical management. Additional genes, such as the *SDH* genes *SMAD4, CDKN2A, NF1,* and *BMPR1A*, are used in clinical management but may not have consensus guidelines.
[b]Biallelic mutations manifest as a recessive disorder with additional disease risks.

with ovarian cancer undergoing testing using a 49-gene panel.[8] However, 22 additional mutations in 10 genes were also identified, including *TP53* (3 mutations) of Li-Fraumeni syndrome and *MSH6* (2 mutations) of Lynch syndrome. Notably, estimates of ovarian cancer risk and clinical guidelines for prevention are limited for most of these genes except *BRCA1/2* and *MSH6*, thus offering providers and patients little direction on how to factor the discovered mutations into the assessment of personal and family risks, or into recommendations for preventive efforts to mitigate those risks.

Panel gene tests may identify mutations in hereditary cancer risk genes that are both anticipated and not anticipated by the personal and family history reported by the patient. The discovery of germline *TP53* mutations in patients with ovarian cancer,[8] and other research studies identifying mutations in genes that do not clearly match the family pedigree, suggest that current understanding of the cancer genotype-phenotype may still be incomplete because of previous testing preselected in families meeting classic high-risk criteria for a particular syndrome.[9–11] Thus, the interpretation of these incidental findings in family cancer risk assessment and management is evolving. Atypical family presentations or limited family structure (eg, very small family size, adoption) can also make it difficult to rely on family history alone to guide testing choices. Although some mutations may have a substantial impact on cancer risk recommendations, others will be more difficult to interpret clinically because of a lack of correlation with family history (eg, *BRCA1/2* mutation in a family with hereditary colorectal cancer) or a lack of evidence-based recommendations for management (eg, *BRIP1* mutations).

Hereditary cancer risk gene panels also offer the ability to more readily examine the potential co-occurrence of mutations in high- and moderate-penetrance genes in families. Studies have found that common moderate-risk genes, such as *ATM* or *MUTYH*, may coexist in families discovered to have another hereditary cancer risk mutation, such as in *BRCA1/2*.[9] Although little is currently known about how these genes may interact in determining breast cancer risk, the detection of co-occurrence of mu-

**Table 2 Clinical Advantages and Disadvantages of Panel Testing for Cancer Susceptibility**

| Advantages | Disadvantages |
|---|---|
| ***Increased Clinical Efficiency*** | ***Identification of Mutations and Variants in:*** |
| • Quicker turnaround time than sequential testing | • Moderate-penetrance genes |
| • Testing approach based less on a stringent phenotype | • High-penetrance genes unrelated to clinical features in patient and family members |
| • Informed consent and sample collection at one clinic visit | ***Clinical Utility Not Yet Studied*** |
| • One time insurance review | • Some commercial health insurance plans designate panels as "investigational" |
| ***Potential Cost Savings*** | • Lack/unclear insurance coverage |
| • Lower per-gene cost | • Lack of evidence-based management strategies for many of the rare syndromes or gene mutations |
| • Identification of co-occurrence of mutations in different genes | ***Increased Prevalence of VUS*** |
| ***Improved Detection of Cancer Susceptibility Mutations in Patients With:*** | • Many genes on panels have not been widely tested in populations |
| • Atypical cancer phenotypes | • Commercial laboratories use separate processes to discern whether variant is clinically actionable |
| • Absent family history information (adoption) | • Additional burden on clinical staff to store and track VUS results |
| • Family history not meeting standard testing criteria | • Patients and healthcare providers may mistakenly manage VUS as deleterious mutations |
| • Family history meeting >1 cancer family syndrome criteria | ***Technology*** |
| ***Technology*** | • Methodology rapidly changing, which pressures laboratory question/answer and test development processes |
| • Constant improvements in gene capture and analysis | • Laboratory-specific processes may limit the interrogation of specific regions |
| • Flexible platform that can add additional genes | • Difficult to compare analytical utility across several laboratories |

Abbreviation: VUS, variants of unknown significance.

tations from gene panels in families may contribute to future understanding of interactions of genes with high- and moderate-penetrance to cancer risk.[12–14]

Finally, it must be appreciated that multigene panels may also save time and reduce costs, even if counseling burdens are higher. Although patients with tumors associated with multiple syndromes (eg, ovarian) may have required multiple tests and counseling visits in the past, these same patients may now be counseled and tested once, and, if out-of-pocket copays for genetic tests exist, also pay these once rather than across multiple tests or clinical visits. Other burdens, such as lost work time and "testing fatigue," will also be improved with the panel approach.

## Potential Disadvantages of Gene Panel Testing for Inherited Cancer Risk Assessment

Potential disadvantages to gene panel testing must also be considered in inherited cancer risk assessment (Table 2). One consideration is the necessity of sequencing genes on a panel that would not have been chosen to test based on the clinical phenotype or pedigree. Here, the difficulty occurs when mutations are discovered in genes that are predicted to be unrelated to the clinical presentation (eg, a 40-year-old woman with colorectal cancer and a mutation in *BRCA2*). The appropriateness of counseling this young woman to consider breast MRI, risk-reducing surgery, or testing of family members for the *BRCA2* mutation in the setting of concern for colorectal cancer risk remains difficult to determine.

As noted earlier, many panels recently made commercially available to providers also sequence genes about which clinical data for risk management may be limited, including moderate-penetrance genes. Providers may want to extrapolate risk-reduction strategies from more extensively studied genes (eg, *BRCA1/2*) that impart cancer risk.[15] However, evidence supporting clinical recommendations based on mutations in moderate-penetrance genes is lacking. For patients, the receipt of uncertain genetic risk information generated from a panel gene test may be particularly difficult to understand and accept.[16–18] High-risk patients and family members in particular may feel inclined to embark on a screening or risk-reducing approach in light of the genetic findings, even in the absence of clear evidence for benefit of these interventions, and expose themselves to unnecessary risk. The discovery of mutations in moderate-penetrance genes such as *ATM* or in single alleles of genes such as *MUTYH*, which are thought primarily to increase cancer in a recessive manner, generates a different sort of uncertainty regarding how best to tailor current clinical prevention recommendations.[18] A further challenge is the impact on family members of patients in whom variants of uncertain significance (VUS) or alterations in moderate-penetrance genes are identified. Laboratory reports often include a recommendation to test family members to gain insight into the role of the alteration in familial cancer risk. However, this can increase anxiety in family members regarding cancer risks and can pose challenges to genetic specialists regarding specific testing and management recommendations based on positive or negative results.

Gene panel testing may also have important technical disadvantages. In some circumstances, mutations that would be detectable using traditional single gene analytic methods may be missed using NGS technologies. If high clinical suspicion remains for a particular syndrome after negative panel test results, consultation with the testing laboratory and/or additional targeted genetic testing may be warranted. Additionally, laboratories may also differ on their determination of variant pathogenicity (benign, uncertain significance, or deleterious), in their policies regarding updating providers about changes in interpretation of variants, and in their policies regarding making the pooled deidentified results of testing publicly available to providers to more effectively guide clinical practice. Members of the same family testing in different laboratories for the same mutation may receive differing result interpretations, leading to confusion in cancer risk management.

A final important risk of gene panel testing is the higher rates of identifying VUS currently associated with these newer tests. VUS are clinically troubling for several reasons, including that many providers and patients make the mistake of assuming that a particular VUS is responsible for disease risk in a family, leading to misguided risk-reducing recommendations. VUS represent data about natural variation in a gene sequence, and, with time and sequencing experience, most are reclassified as benign.[19] However, a fraction of VUS will be reclassified to disease-causing, highlighting the need for providers to track VUS reclassification and inform patients, which requires time and resources often for many years.

## Potential Clinical Application of Gene Panel Testing and Counseling Considerations for Inherited Cancer Risk Assessment

### Clinical Scenarios Conducive to Gene Panel Testing

Although patients with a known mutation in the family should have testing focused on the familial mutation rather than undergoing larger gene panels, specific clinical scenarios may particularly benefit from the ability to sequence multiple genes simultaneously to assess for disease-associated mutations:

- Personal medical and/or family cancer history meets criteria for more than one hereditary cancer syndrome
- Family cancer history does not meet established testing guidelines, but consideration of inherited cancer risk persists and an appropriate panel is available
- Individuals with multiple cancer diagnoses
- Individuals concerned about cancer predisposition for whom family cancer history is limited or unknown
- Second-line workup for inherited cancer risk when first-line evaluation has been inconclusive

All discussions must include the risks and benefits of gene panel testing in a genetic counseling setting, with informed consent reflecting the discussion.

### Choice of Laboratory for Testing

Choice of laboratory for performing gene panel sequencing is also important. Several laboratories offer gene panel tests for breast and colon cancer risk, and fewer offer panels for more rare cancers or conditions, such as kidney cancer or paraganglioma. Laboratories are also emerging that allow clinicians to choose genes and create a custom panel. Table 3 lists factors to consider when choosing a testing laboratory. Laboratory experience and familiarity with NGS technologies, variant reclassification processes, test sensitivity, and confirmation of VUS or positive results with a second testing technology are some technical considerations. The availability of patient and clinician services are also common considerations when clinical laboratories are considered for testing. Laboratories that provide preverification services and a maximum out-of-pocket cost help patients make decisions about test affordability. Several laboratories also offer financial assistance programs for underinsured or uninsured patients, which may be important for the former or those with strong personal or family histories that do not meet standard testing criteria set by their private or federal insurer.

### Genetic Counseling and Informed Consent Considerations

The role of genetic counseling and thorough informed consent discussion in the era of gene panel testing for inherited cancer risk is vital for patients to make informed decisions about genetic testing. Pretest counseling should educate patients on possible test options; test results; risks, benefits, and limitations of testing; and implications for both the patient and family members[7,20] (Table 4). Briefly, patients should be informed of the option of single-gene or syndrome-specific testing, which may more quickly identify actionable mutations, particularly when pending a treatment decision. Patients should also be informed about the various panels available for their specific cancer concern. Penetrance of genes on various panels should be discussed, such as panels that include only high-penetrance genes versus both high- and moderate-penetrance genes. Additionally, the uncertainty of medical management based on alterations identified in moderate-penetrance genes or VUS must be discussed with patients and included in informed consent discussion before a specific gene panel is ordered.

**Table 3 Factors to Consider When Choosing a Laboratory for Gene Panel Testing**

- Maximize likelihood of finding mutations in genes of interest
  - ▸ Sensitivity
  - ▸ Average number of reads per base pair
  - ▸ Minimum number of reads per base pair
  - ▸ Low read confirmation by Sanger sequencing
  - ▸ Variant confirmation by Sanger sequencing
  - ▸ Number of base pairs into intronic region
  - ▸ Base pair size of insertions/deletions
- Laboratory with experience in genetic testing
- Financial assistance program
- Preverification of benefits and maximum out-of-pocket cost
- Transparency in variant classification methods
- Provides clear and accurate test report (including variant description)
- Public availability of variant data
- Rates of variants of uncertain significance
- Variant reclassification program
- Clinician recontact protocol with reclassified variants

Potential test findings should also be discussed and included in counseling and the informed consent document. Patients often expect a clear positive or negative result from testing, and even pretest counseling addressing the potential for an unclear result may be challenging for a patient to understand.[21] Positive results in suspected high-penetrance genes that correlate with the individual and/or family history are more straightforward and can inform medical and cancer risk management decisions. However, questions may arise regarding appropriateness of medical management if a genetic mutation is identified in a family that does not manifest the typical cancer diagnoses. For example, individuals with mutations in the *CDH1* gene may strongly consider prophylactic gastrectomy because of limitations in screening for diffuse gastric cancer.[22] However, the appropriateness of this may be questionable if the family history is negative for breast or gastric cancers. Patients must be aware of such potential findings at pretest counseling and during the informed consent process.

Expectations and plans for recontact should be explicitly stated, including encouraging patients to contact their clinicians periodically for follow-up and to keep contact information current.[23] Reiterating recontact plans at the time of results disclosure is recommended, because lack of patient clarity on this issue could result in provider liability. This is particularly relevant to VUS reclassification and new research findings of cancer risks from mutations in moderate-penetrance genes. Many laboratories review their VUS data on a regular basis and will follow up with the ordering clinician if results are reclassified. Some laboratories will only contact the clinician if results are reclassified as actionable, and not if the result is downgraded to a benign polymorphism. Again, these issues need to be included in the informed consent document.

**Table 4 Pretest Discussion Points**

- Limitations in cancer risk estimates for moderate-risk genes
- Increased potential for VUS
- Limitations of medical management options for moderate-penetrant gene mutations and VUS
- Plan for recontacting regarding updates to VUS findings
- Potential limitations of result interpretation for family members
- Potential to identify mutations conferring risk for unexpected cancer syndrome in a family
- Potential limitations in cancer screening and prevention options
- Potential for recessive disorders

Abbreviation: VUS, variants of unknown significance.

An important issue for patients of reproductive age is the occurrence of mutations in genes that cause autosomal recessive conditions, such as ataxia-telangiectasia, Nijmegen breakage syndrome, and Fanconi anemia. This could be challenging to health care providers who are not as knowledgeable about cancer risks in the pediatric population. Carriers of *ATM, NBN, PALB2,* and other recessive gene mutations should be made aware of the possibility of disease risk in their children if the other parent carries a mutation in the same gene. Although these syndromes are individually rare, carrier and prenatal testing options are available.

## Conclusions

The field of gene panel testing for inherited cancer risk assessment is in rapid evolution, with significant potential to inform cancer risks for individuals and families. With this promise comes the potential to uncover genetic alterations that may lead to uncertainty regarding cancer risk and management decisions. Given the potential issues for patients and their families, gene panel testing for inherited cancer risk is recommended to be offered in conjunction or consultation with experienced genetics professionals, such as genetic counselors or geneticists, as an integral part of the evaluation and testing process. Patients, providers, and researchers need to be engaged in this era of cancer genetics and genomics to usher in personalized cancer risk assessment with attention to medical, ethical, legal, and social issues.

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