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Avalon's Proper NGS Panel Coding Initiative—Decreasing Cost Without Compromising Quality

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Abstract

Recent advances in nucleic acid technologies, often referred to as next generation sequencing or NGS, allow for rapid, parallel testing of multiple genes or even an entire genome. NGS panel tests can provide patients clinically actionable data since targeted therapies are now available. The American Medical Association (AMA) has commissioned specific Current Procedural Terminology (CPT®) codes for these genetic panels. Unfortunately, contrary to AMA guidelines, many labs have continued to either stack or unbundle the individual test codes, resulting in higher costs to patients and/or payers. Avalon has conducted a study with the objective to gauge how education and quality assurance (QA) processes affect correct implementation of clinical practice coding guidelines. Using administrative prior authorization data from a single network provider from 1/2018 to 10/2019, descriptive statistics were conducted, and service unit utilization was tracked over the study period by procedure code. Over the course of this study, utilization by approved units of genetic sequencing is comparable; however, a decrease in utilization in the inappropriate code (81162) occurs as usage of the appropriate NGS panel codes (81432/81433) increases. Additionally, the denial disposition breakdown shows that denials are due primarily to lack of medical necessity (86.8%), and thereby not from inappropriate filing or administrative reasons. As the education endeavors progressed, a decrease in the number of denials due to a lack of medical necessity also occurred. A cost analysis shows that unbundling the panel codes can cost several thousands of dollars more to the patient and/or payer without providing any additional clinical benefit. Taken together, education and QA processes can positively redirect providers and laboratories to follow AMA coding practice guidelines while providing patients with clinically appropriate genetic testing without increasing coverage denials due to inappropriate filing or other administrative reasons. Therefore, trends in decrease denials can be attributed to education and QA measures, ensuring correct coding and medical necessity as described by medical policy.

Cancer in the U.S.

According to the Centers for Disease Control and Prevention (CDC) and the U.S. Cancer Statistics (USCS), "In 2016, the latest year for which incidence data are available, 1,658,716 new cases of cancer were reported, and 598,031 people died of cancer in the United States. For every 100,000 people, 436 new cancer cases were reported and 156 died of cancer. Cancer is the second leading cause of death in the United States, exceeded only by heart disease. One of every four deaths in the United States is due to cancer[12]." Genetics, socioeconomic status, access to healthcare and preventive services, environmental factors, and geography have been linked to cancer prevalence[12-20]. For example, in the U.S. alone based on the 2016 data, the cancer rates vary from state to state with the lowest occurring in New Mexico (359.4 per 100,000) and the highest rate in Kentucky (509.7 per 100,000)[12].

Breast cancer rates in females in the U.S. are still increasing (126.8 per 100,000 in the 2020 Annual Report to the Nation on the Status of Cancer[21]). Female breast cancer is second only to lung cancer in cancer-related deaths in the U.S. with a rate of 20.0 per 100,000 versus 38.5 for lung and bronchus cancer, and it is the number one new cancer diagnosis[12] **(Figure 1)**.

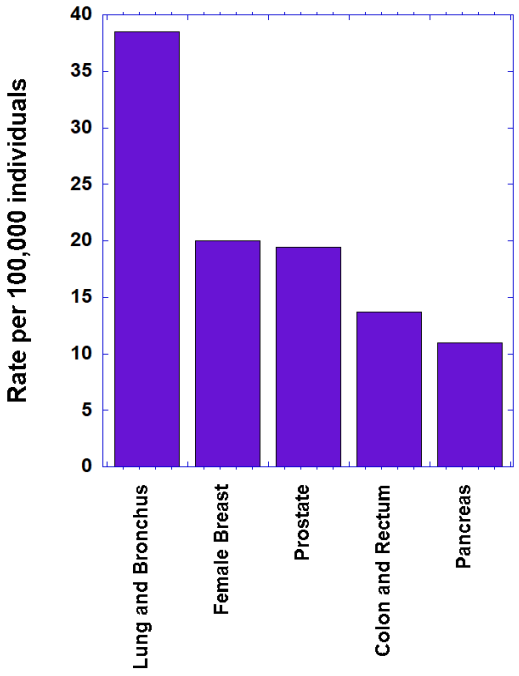


Figure 1: *Top 5 Cancers By Rate of Cancer Deaths in U.S. in 2016.* These data are based on the data of the U.S. Cancer Statistics Working Group of the Centers for Disease Control and Prevention and the National Cancer Institute, published in 2019[12].

Genetic Testing Can Provide Clinically Actionable Data

As previously stated, cancer, in general, can be affected by genetics **(Table 1)**. For example, *BRCA1* and *BRCA2* testing is included in several NCCN algorithms, including breast, ovarian, and prostate cancers[22-24]. *BRCA1* and *BRCA2* are tumor suppressor genes that are involved in homologous recombination repair of double-strand DNA breaks[25]. Both genes are very large (occupying about 70 kb), encoding a combined total of 49 exons. A loss of function on either gene increases cancer risk[26]. *BRCA1* regulates c-Abl kinase activity with a loss of *BRCA1* resulting in a constitutively activated c-Abl kinase whereas *BRCA2* regulates Rad51, another protein involved in DNA damage repair[27].

Different regions of mutation within the gene may confer different types of disease risk. For example, *BRCA2* has an area called the ovarian cancer cluster region (OCCR) in which mutations predispose the patient for ovarian cancer. Mutations outside the OCCR are more likely to result in breast cancer compared to mutations in the OCCR. On *BRCA1*, mutations closer to the 3' end of the gene may result in higher risk than mutations closer to the 5' end [28]. Other gene defects that affect homologous recombination include hypermethylation of *RAD51C* or *ATR* mutation. However, these are considered to have a phenotype of "BRCAness" and behave like *BRCA*-deficient genes even if the *BRCA* gene itself is normal [25].

The overall prevalence of disease-related mutations in these genes is estimated to be 1 in 300 for *BRCA1* and 1 in 800 for *BRCA2* [29]. Although the probability of cancer development in carriers is variable, estimates of penetrance in individuals with a pathogenic variant in *BRCA1* or *BRCA2* range from 46% to 87% lifetime risk for breast cancer, and 16.5% to 63% lifetime risk for ovarian cancer [30]. *BRCA1* and *BRCA2* mutations account for about 5 – 10% of breast cancers and 10 – 18% of ovarian cancers [25]. *BRCA* mutations are inherited in an autosomal dominant fashion and are highly penetrant[31]. Recent studies have also implicated *BRCA* mutations with increased risk for male breast cancer although additional studies are needed[32-34].

Many genes besides *BRCA1* and *BRCA2* have been linked to hereditary breast cancer-related disorders, including but not limited to *CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11,* and *TP53* **(Table 1)**. These genes regulate cell growth in varying ways. For example, the protein encoded by *CDH1*, epithelial cadherin, acts as a tumor suppressor protein by transmitting chemical signals internally as well as being an adhesion protein to control cell size[1]. *MLH1, MSH2,* and *MSH6* are all components of the DNA mismatch repair pathway (MMR) and are also associated with Lynch Syndrome[35]. The protein PALB2 forms a complex along with BRCA1 and BRCA2 proteins within the homologous recombination repair pathway (HRR), and it aids in DNA polymerization at collapsed replication forks by localizing POLH, a polymerase, to the site[2]. *PTEN* encodes for a ubiquitous tumor suppressor enzyme that removes phosphate functional groups from proteins and lipids. In doing so, this enzyme serves an important role in several different cellular cascades, including apoptosis and angiogenesis, both of which are crucial in carcinogenesis[3]. On the other hand, *STK11* encodes for a kinase, which adds a phosphate group to substrates within cellular transduction pathways, such as apoptosis[4]. *TP53* encodes for a nuclear protein called p53, which typically acts as a tumor suppressor, and it is involved in many cellular processes, including regulating "various metabolic pathways, helping to balance glycolysis and oxidative phosphorylation, limiting the production of reactive oxygen species, and contributing to the ability of cells to adapt to and survive mild metabolic stresses[36]." However, both gain-of-function and loss-of-function mutations of *TP53* can be carcinogenic[37]. It should be noted that many of these genes, including *BRCA2*, *PALB2, TP53, STK11*, and many more have recently been associated with male breast cancer as well although additional research is needed[38,39].

Gene	Gene Name
BRCA1	BRCA1‡
BRCA2	BRCA2‡
CDH1	cadherin 1
MLH1	mutL homolog 1
MSH2	mutS homolog 2
MSH6	mutS homolog 6
PALB2	partner and localizer of BRCA2
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PTEN	phosphatase and tensin homolog
STK11	serine/threonine kinase 11
TP53	tumor protein p53

Table 1: *Representative Genes Associated with Breast Cancer*. Mutations within these genes are associated with an increased risk of breast cancer. The gene names are from the Genetics Home Reference of the National Institutes of Health[1-11]. ‡BRCA1 and BRCA2 are now recognized as official gene names but have historically been referred to as breast cancer 1 and breast cancer 2, respectively.

Identification of carrier status is important to guide management of cancer and to identify unaffected women with a *BRCA* mutation who will benefit from enhanced surveillance, tailor care to improve outcomes, and more efficiently use health-care resources. This has the potential to have a significant individual and population health impact on morbidity and mortality if these women adhere to guidelines for managing cancer risk [40].

Individuals desiring to know their susceptibility to develop cancer later in life are also seeking genetic testing. At times, family history of these individuals may indicate a possible genetic predisposition, but other times the family history may be limited or even unknown. Depending on their status, these individuals may choose different therapies ranging from

active surveillance to even bilateral prophylactic mastectomy (BPM)[41]. Recent studies have indicated that other less radical procedures, such as nipple-sparing mastectomy (NSM), which offer superior cosmetic outcomes than BPM can also be used as potential prophylactic measures[42]. Many tests are commercially available; even at-home DNA tests, such as 23andMe, offer kits that include testing of select variants of *BRCA1* and *BRCA2*[43]. Direct-to-consumer testing, however, does not include all possible known variants or genes and should never be used for diagnosis. According to the FDA, "The test report does not describe a person's overall risk of developing any type of cancer, and the absence of a variant tested does not rule out the presence of other variants that may be cancer-related. This test is not a substitute for visits to a healthcare provider for recommended screenings or appropriate follow-up and should not be used to determine any treatments[44]."

NGS panel testing results can often include variants of uncertain significance (VUS). These VUS can confound the results of genetic testing and can cause anxiety in the patient. A 2017 study on the clinical decision-making in patients who undergo *BRCA1* or *BRCA2* testing show that patients who receive results containing VUS were more likely to undergo BPM. The same study show that individuals with cancer who have results containing VUS, though, have similar rates of surgery as average-risk breast cancer patients[41]. A 2018 study has shown that cosegregation analysis can help decrease the number of VUSs from panel testing. "Cosegregation analysis was performed for 13 VUSs in 11 kindreds. Seven VUSs (53.8%) did not cosegregate with breast/ovarian cancer in the family, which provided evidence against their role in cancer clustering in those families. Among the 6 cosegregating VUSs, for two (*BRCA1* c.5152+2T>G and *BRCA2* c.7975A>G) additional evidence exists from databases and in silico tools supporting their pathogenicity, which reinforces the hypothesis they may have had a predisposing effect in respective families[45]." Such analysis may be helpful in decreasing anxiety or in guiding possible therapeutic approaches.

Interestingly, a recent 2018 study of 362 males seeking *BRCA* testing in a Breast Cancer Risk Evaluation Clinic setting show that 80.2% of males who discovered that they were mutation carriers opted for active surveillance and successfully followed up for the entire duration of the study (36.9 months). The surveillance methodology included annual oncology, urology, and dermatology screenings as well as specific surveillance protocols based upon the individual's specific mutation, such as colon screening for *CHEK2* 1100delC carrier mutations. Three individuals did die during the study—two from advanced gastric cancer and one with disseminated adenocarcinoma[46]. This study does show that knowledge of carrier status may help increase active surveillance participation in certain populations.

NGS testing can be used to help guide possible targeted therapy. Targeted therapy or precision medicine treats the disease or condition based on an individual's genetic variability, lifestyle, and environment rather than prescribing a single treatment for a disease[47,48]. For example, *BRCA*-deficient cancers are often targeted for a class of drugs called poly(ADP-ribose) polymerase (PARP) inhibitors, which target enzymes responsible for the base excision repair pathway. A cell can survive with the loss of either the base excision repair pathway or the homologous recombination mechanism, but not both. Since *BRCA*-deficient cells already

have a faulty homologous recombination mechanism, the *BRCA*-deficient cell dies when the PARP inhibitor shuts down the base excision repair pathway. *BRCA*-deficient cells have been shown to be affected 1000 times more by these PARP inhibitors than wild-type cells [25].

Phosphatidylinositol 3-kinase (PI3K) is encoded by the *PIK3CA* gene, and a gain-of-function mutation associated with this enzyme activates multiple signalizing cascades, including the *PI3K/AKT/mTOR* pathway. The use of PI3K inhibitors alone had modest success; however, a PI3K inhibitor, such as alpelisib, plus fulvestrant results in considerable synergy in overcoming resistance to antiestrogen therapies[49,50]. The FDA, in fact, has even approved a screening test specific for the detection of known *PIK3CA* mutations that respond to alpelisib treatment. From the FDA website: "The therascreen *PIK3CA* RGQ PCR Kit is a real-time qualitative PCR test for the detection of 11 mutations in the phosphatidylinositol 3-kinase catalytic subunit alpha (*PIK3CA*) gene (Exon 7: C420R; Exon 9: E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R; and Exon 20: H1047L, H1047R, H1047Y) using genomic DNA (gDNA) extracted from formalin-fixed, paraffin-embedded (FFPE) breast tumor tissue or circulating tumor DNA (ctDNA) from plasma derived from K_2EDTA anticoagulated peripheral whole blood taken from patients with breast cancer"[51].

Another example of possible targeted therapy is loss-of-function *PTEN* mutation, resulting in an altered downstream AKT/mTOR pathway, in individuals with metastatic triple-negative breast cancer[50]. Capivasertib plus paclitaxel combination therapy has an increased PFS [progression-free survival] (9.3 months versus 3.7 months) as compared to the intent-to-treat population (5.9 months versus 4.2 months). This same study, though, shows an even greater effect using ipatasertib with paclitaxel in lieu of capivasertib (9.0 months PFS)[50,52].

NGS Facilitates Rapid Sequencing in Parallel

For conditions with a known family history, single gene sequencing using traditional methodology, such as Sanger sequencing, is logical. For other conditions, it may be more prudent and cost-effective to use a method capable of targeting multiple sequences simultaneously. NGS allows for the rapid sequencing of multiple strands of DNA. It is not limited to one specific type of test; rather it encompasses numerous technologies that produce swift, high-volume sequencing. NGS can be used to sequence multiple genes, the exome, or even the entire genome. This is opposed to the traditional Sanger sequencing, which is more useful for sequencing a specific gene [53,54].

The NGS procedure typically includes the following steps: first the patient's DNA is prepared to serve as a template, then DNA fragments are isolated (on solid surfaces such as small beads) where sequence data is generated, then these results are compared against a reference genome. Any DNA sample may be used if the quality and quantity of that sample are sufficient, but the methods of library generation and data analysis often vary from panel to panel and may be proprietary. Evaluating the results of a gene panel typically requires

some expertise in bioinformatics. Since NGS reports data on any variants found, great care must be taken to evaluate these gene variants, especially variants of unknown significance (VUS) and secondary findings [53,55]. The clinical utility of NGS includes situations where multiple genes cause the same phenotype, other candidate genes were found to be normal, and sequencing individual genes would not be timely or cost-effective[53].

Panels that sequence multiple, specified genes are referred to as "targeted panels" and may range from 5 to over 1000 genes. Targeted panels are generally more cost-effective than whole exome or whole genome sequencing and are useful for conditions where many different genes may cause a disease phenotype. For example, nonsyndromic hearing loss may be caused by variants in over 60 genes and sequencing each gene individually would not be cost-effective. Many companies have developed a wide variety of gene panels. From the FDA-approved MSK-IMPACT to well-validated proprietary panels, many different options of panel testing are available [53].

Findings such as pathogenic variants are traditionally confirmed by Sanger sequencing, which is considered the gold standard of gene sequencing (>99.99% accuracy). NGS has been shown to compare favorably to Sanger sequencing. In a study performed by Strom et al, 110 single-nucleotide variants (SNVs) were found by NGS, with 103 of those SNVs meeting the minimum quality score threshold of 500 set by the lab and 7 falling below this threshold. However, 109 of the 110 total SNVs were validated by Sanger sequencing [56]. Another study focusing on the agreement between Sanger sequencing and NGS results found only 2 variants out of 5800 that did not have cross-method agreement. Overall, the agreement rate was 99.965%. The authors concluded that a single round of Sanger sequencing was "more likely to incorrectly refute a true-positive variant from NGS than to correctly identify a false-positive variant from NGS" [57].

Discussions of utility may also revolve around what is done with the findings of a gene panel. For instance, a study by Zehir et al focused on the MSK-IMPACT gene panel. This panel of 410 cancer-related genes was used to sequence 10945 tumors from 10336 patients. 36.7% (3792/10336) of these patients were found to have a "clinically actionable" gene variant, such as *TP53* and *KRAS*. Of these, 527 patients were enrolled in clinical trials [58]. NGS has also helped provide diagnostic information to patients. A study focusing on 382 patients with a previously undiagnosed condition used NGS technology to diagnose 98 patients with exome or genome sequencing, allowing for changes in diagnostic testing, treatment, and genetic counseling. A total of 31 new syndromes were defined as well [59].

Surrey et al evaluated the clinical utility of a custom NGS panel for pediatric tumors. Sequencing was performed on 367 pediatric cancer samples. The authors found that results from the panel testing were "incorporated successfully into clinical care" for 88.7% of leukemias and lymphomas, 90.6% of central nervous system (CNS) cancers, and 62.6% of non-CNS solid tumors. A diagnosis change occurred in 3.3% of cases, and 19.4% of patients had variants requiring further germline testing [60].

Financial Impact of Unbundling Panel Codes

The American Medical Association (AMA) has issued many Current Procedural Terminology (CPT®) codes for genomic sequencing panels, which include those utilizing NGS technology. These panel codes each consist of "discrete genetic values, properties, or characteristics in which the measurement or analysis of each analyte is potentially of independent medical significance or useful in medical management[61]." Unlike the multianalyte assays with algorithmic analyses (MAAAs), these panel codes cannot consist of algorithmic risk scores or any additional values other than their individual component test results. Examples of these genetic panel test codes include those centered around ethnic groups (such as 81412 Ashkenazi Jewish-associated disorders), panels comprised of genes associated with a related disorder or spectrum of disorders (such as 81442 Noonan spectrum disorders), and genomic-wide methodology panels (such as 81465 Whole mitochondrial genome large deletion analysis panel) to name a few. The AMA had two additional *BRCA*-based panel codes—81211, *BRCA1/BRCA2* full sequence analysis and common variants, and 81213, *BRCA1/BRCA2*, uncommon variants — that were retired in 2019 and replaced with more appropriate 81432 and 81433 codes that include breast cancer-related genes in addition to *BRCA1* and *BRCA2*[61]. [For a full list of CPT® codes with their long descriptions, please see the Supplemental Table 1 within the Supplemental Information.]

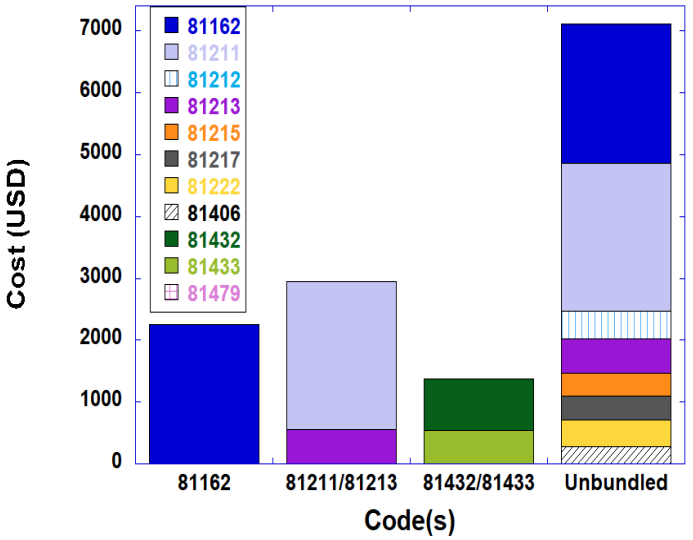


Figure 2: Cost Analysis of Unbundling NGS Panels. A comparison of financial cost between unbundling codes and appropriate NGS panel codes based on the 2018 CMS Procedure Cost Per Unit. [Code 81479 was not included due to variable reimbursement rates.] Please see supplemental table for code descriptions.

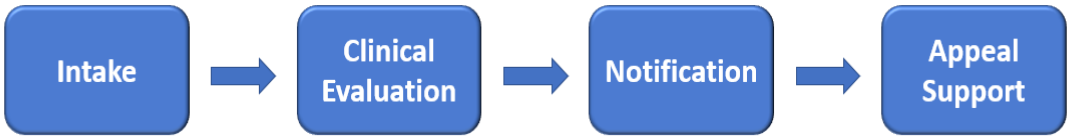
Unfortunately, contrary to AMA guidelines, many labs have continued to either stack or unbundle the individual test codes rather than use an appropriate NGS panel CPT® code, resulting in higher costs to the patients and/or payers. Using an AMA-issued procedure code for the gene panel test can decrease costs. As depicted in the example in **Figure 2,** when unbundled, *the accumulated cost is several thousands of dollars* based on the 2018 CMS procedure cost per unit whereas the appropriate 81432/81433 combination ***is less than $1500***. Prior to the retirement of 81211 and 81213 in 2019, combined testing cost around $3000. Code 81162 does cost around $2200; however, it includes testing only for BRCA1 and BRCA2 whereas the newer 81432/81433 codes established in 2019 must include

not only BRCA1 and BRCA2 but also additional genes associated with breast cancer. It should even be noted that in the example given in **Figure 2**, code 81479, an unlisted molecular pathology code frequently encountered, was not included in the cost analysis since it has a variable CMS reimbursement rate so the unbundled accumulative cost would be over $7000.

Education and Quality Assurance Measures Can Positively Redirect Labs and Providers to Follow AMA Guidelines

The objective of this study is to gauge how education and quality assurance (QA) processes affect correct implementation of clinical practice coding guidelines. The overarching goal of quality assurance is that the ordering provider is receiving the testing they requested for their patient in a cost-effective, code-appropriate manner provided that the test is medically necessary according to medical policy. Avalon has a robust Prior Authorization process that oversees genetic testing management (GTM), including NGS testing, as depicted in **Figure 3**.

Figure 3: Avalon Prior Authorization Process



Key Features:

1. **Test Identification:** *Analyte-specific evaluation of molecular panel and unlisted codes*
2. **Panel Evaluation:** *Promotes appropriate use of lab-specific molecular panels (elimination of unsuitable code stacking and/or excessive panels)*
3. **Decision Detail:** *Accessibility & Easy to understand*

The four principle steps of the Prior Authorization process consist of intake, clinical evaluation, notification, and appeal support. In the initial intake phase, a claim is received for prior authorization review. During the clinical evaluation, the nurse or physician reviews the testing the ordering physician has requested, along with the clinical information and records provided, to see if the prescribed NGS panel is medically appropriate. Proactive outreach may also occur if clarity is needed in order for the reviewing physician or nurse to evaluate a claim. The reviewing nurse or physician, for quality assurance, also reviews the claim the rendering provider has submitted to ensure that it matches the NGS panel ordered by the initial provider and that the coding follows AMA guidelines. For an approval notification, both the ordering and rendering provider receives a notification. If a claim is denied, the member, the ordering provider, and the rendering provider all receive detailed notifications. A clearly readable description of why an adverse determination was given is included within the notification. This notification includes the reasons why the ordered NGS panel test is not considered medically necessary. If the denial is solely due to a coding discrepancy, then as part of the education process, the rationale includes how the member may be able to receive approval for testing if the correct procedure codes are supplied on

resubmission. Appeal Support includes educational endeavors to help abate abrasion that health plan clients may receive as well as internal provider and network lab education. This can often include peer-to-peer consultation.

To evaluate the aforementioned effects of education and quality assurance measures on following AMA guidelines, administrative prior authorization data were collected from the Avalon network providers from January 2018 to October 2019. Data were further restricted to a single network provider conducting gene panel testing to demonstrate the course of change in NGS ordering over time from education and QA processes. Descriptive statistics were conducted for the single network provider, and service unit utilization was tracked over this time period by procedure code. During this study, educational materials were created and distributed to providers to guide them on this correct coding initiative. Code analysis was performed to evaluate impact. [For an example of an educational material created and distributed to providers, please see Supplemental Figure 1 of the Supplemental Materials section.]

Prior to the initiation of Avalon's Proper NGS Panel Coding Initiative, an ordering provider may have prescribed an appropriate NGS panel for their patient, but the rendering laboratory could bill the claim as individual codes (such as for *BRCA1 and BRCA2*) or as a different panel altogether (as depicted earlier in **Figure 2**). **Figure 4** shows the utilization of NGS panel testing during the course of this study. In **Figure 4A** the number of claims submitted that were approved as medically necessary as described by medical policy is displayed whereas **Figure 4B** displays the number of claims submitted that were denied. As previously noted, the AMA retired the CPT® codes 81211 and 81213 *BRCA* panel codes in 2019. The red vertical bar in both **Figures**

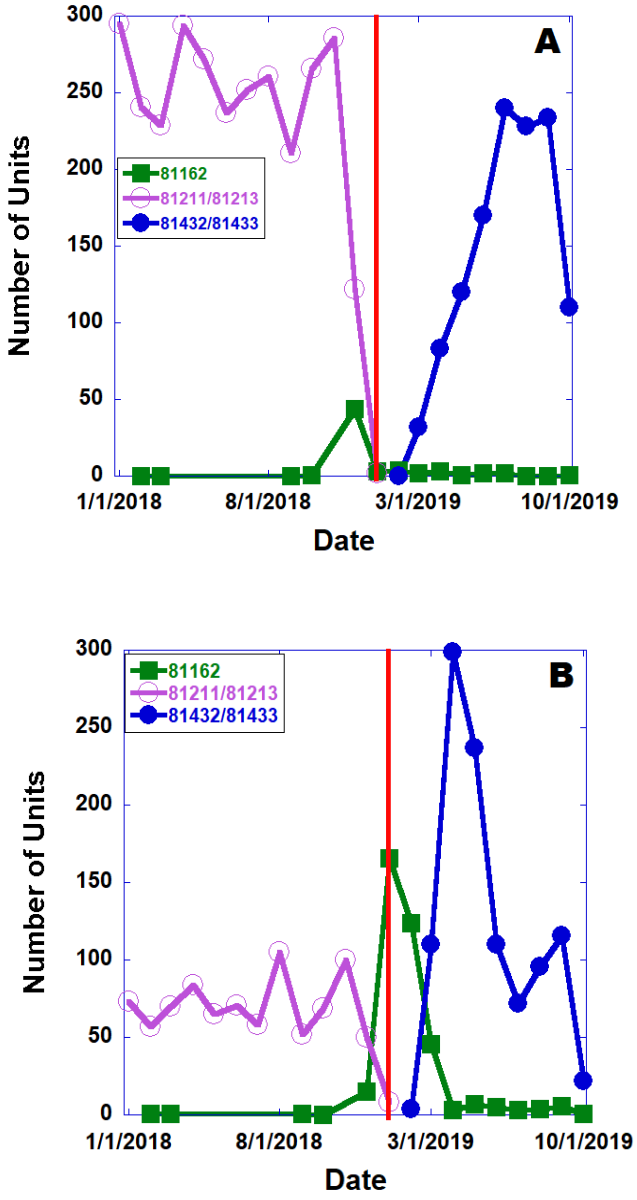


Figure 4: (A) *Approved claims submitted during the course of the study*. The red vertical bar indicates when the codes 81211 and 81213 were retired by the AMA in 2019. **(B)** *Denied claims submitted during the course of the study*. The red vertical bar indicates when the codes 81211 and 81213 were retired by the AMA in 2019.

4A and **4B** indicate when the codes were retired. As seen in **Figure 4**, the use of 81162, a code that includes only detailed analyses of *BRCA1* and *BRCA2*, decreases while the use of the more appropriate panel codes (81432/81433) increases. The NGS panel tests coded by 81432 and 81433 include additional genes beyond only *BRCA1* and *BRCA2*. These data indicate that the QA and education measures have successfully redirected providers to the use of the appropriate NGS panel codes.

Another facet of quality assurance of this initiative focuses on an ongoing evaluation of testing utilization. During the study, among the total cohort, 6559 service units were ordered. Of the total service units, 4248 (64.8%) were paid, and 2311 (35.2%) were denied. In total, 3830 (58.4%) units of procedure codes 81211 and 81213 (both retired in 2019), 2283 (34.8%) combined units of procedure codes 81432 and 81433, and 446 (6.8%) units of procedure code 81162 were performed **(Figure 5)**. This study also inadvertently looked at the effect of the retirement of the 81211/81213 codes had on NGS panel tests claims submitted. It is important to note that the utilization of NGS panel testing did not appreciably decrease. Over the course of this study, utilization by approved units of genetic sequencing before and after the retirement of codes 81211 and 81213 is comparable. This is further supported by the normalized aggregate data where the average monthly total number of claims for 81211/81213 was 294.6 prior to their retirement and the average monthly total number of claims for 81432/81433 was 253.6 after the retirement of the earlier codes **(Figure 5B)**.

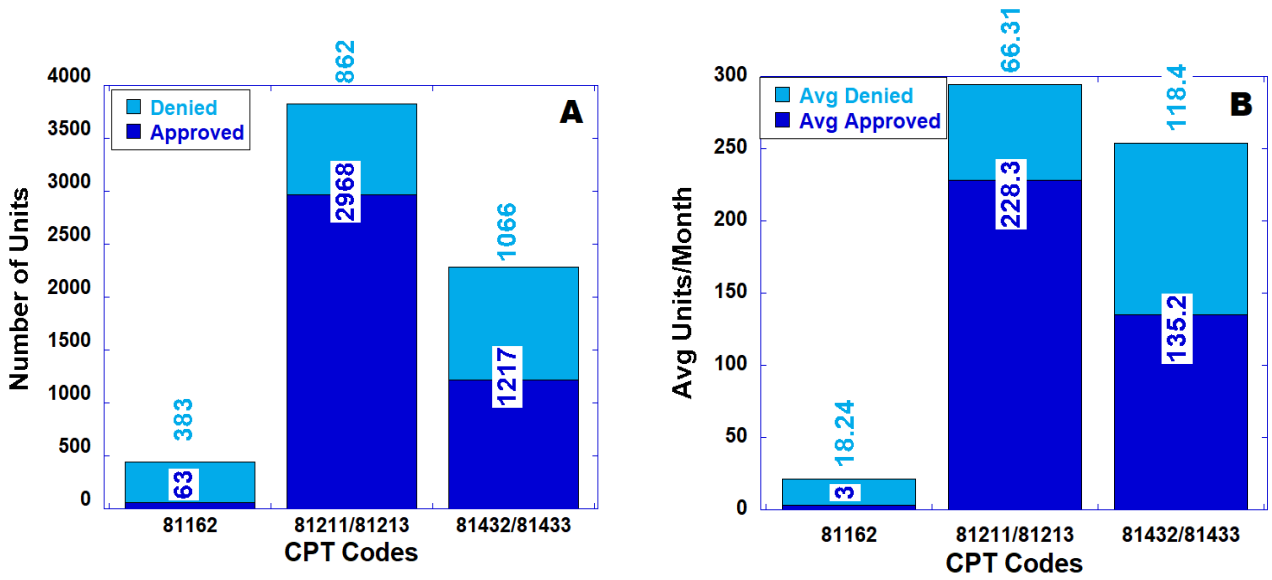


Figure 5: (A) *Aggregate Data.* The total units submitted containing CPT codes included within the purview of the study. The values indicate the total number. **(B)** *Normalized Aggregate Data.* Average units for the duration CPT code was active within study time frame.

Denials Are Primarily Due to Lack of Medical Necessity

As previously stated, quality assurance requires that the ordering provider is getting the testing they ordered for their patient in a cost-effective, code-appropriate manner provided that it is medically necessary according to medical policy. Therefore, it is extremely important to make sure that any protocol or system incorporated does not unintentionally result in an increase in denials of claims that are medically appropriate. To address this, the reasons of the claim denials were recorded over the course of the study, and they could fall into one of four possible categories:

- *Contract Exclusion*: Contract Exclusion refers to lines of business that do not allow for panel testing contractually. During the course of the study as part of the education process, Avalon worked with the network providers to transition to allow for more cost-effect NGS panel testing.
- *Not Medically Necessary*: Not Medically Necessary indicates the individual did not meet the medical criteria required for that particular NGS panel test as deemed by medical policy.
- *Administrative Dismissal (Lack of Timely Filing)*: An administrative dismissal is a retroactive denial due to a claim that did not request a prior authorization for the service in a timely manner.
- *No Decision Rendered*: This category would include any claim that was not rendered a PA review decision by a nurse or physician within the contractually mandated time period.

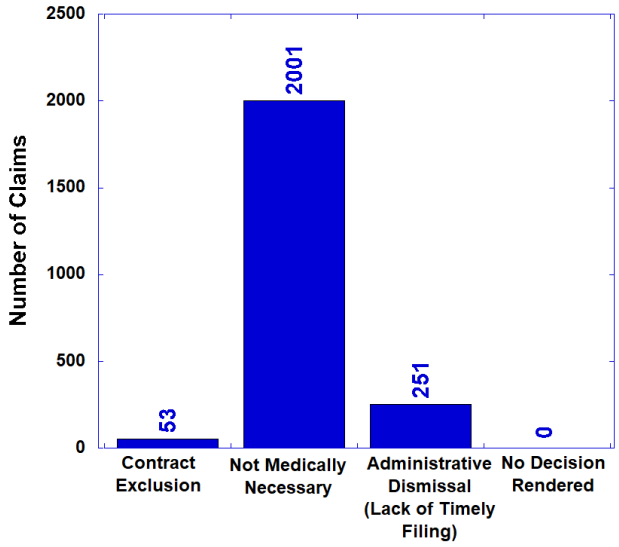


Figure 6: Reasons for Claims Denied. Count of claims denied due to contract exclusion, lack of medical necessity, administrative dismissal, or no decision over study period. The values indicate the total number of each category.

As seen in **Figure 6**, denials were overwhelmingly due to a lack of medical necessity with 2001 claims (or 86.8% of all claims denied). Administrative dismissals, such as lack of timely filing, account for 251 or 10.9% of denials whereas only 2.3% (or 53 claims) were denied due to contract exclusion. No claims were denied due to no decision being rendered by a physician or nurse within the time allotted. These data show that the QA and education measures enforced by Avalon did not result in a large number of denials due to any administrative or contractual reason.

Impact of Education on Denials Due to Lack of Medical Necessity

As part of the QA process, the rate of denials due to a lack of medical necessity were also studied. As can be expected with any change, the uncertainty can cause unanticipated

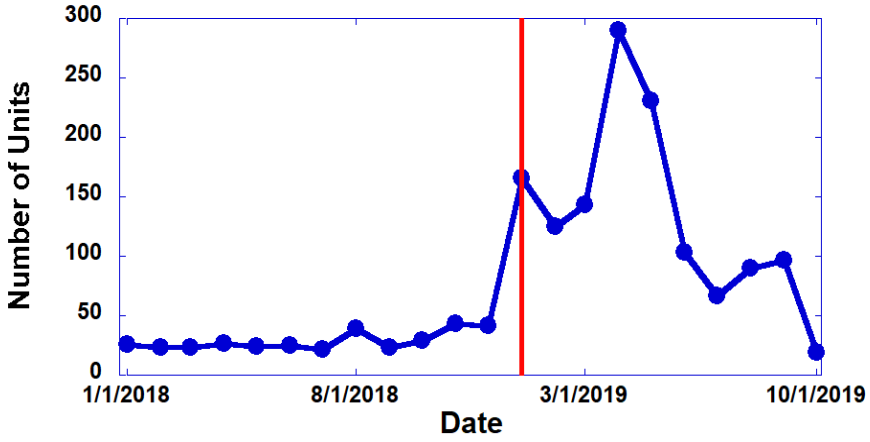


Figure 7: Impact of Education on Denials Due to Lack of Medical Necessity. Count of claims denied due to lack of medical necessity over study period. Vertical red bar indicates the date when CPT® codes 81211 & 81213 were retired by the AMA (2019).

consequences. Whenever the AMA retired codes 81211 and 81213 in 2019, an initial increase in the number of denials due to lack of medical necessity was observed **(Figure 7)**. Interestingly, though, a decrease in the number of denials due to lack of medical necessity followed throughout the remainder of the study as the education and QA measures continued, indicating that the providers were more likely following AMA guidelines. This shows that trends in decrease denials can be attributed to education and QA measures, ensuring correct coding and medical necessity as described by medical policy.

Summary

NGS technology can provide a wealth of knowledge. Targeted therapies are available based on data obtained from NGS panels when they are used according to medical guidelines. Also, genetic testing along with good genetic counseling can help an individual with a known mutation status choose between active surveillance and surgery. Appropriately following AMA guidelines with respect to NGS panel testing can be both more ethical and more cost efficient **(Figure 2)**. Education and QA measures can positively redirect providers and laboratories to follow AMA coding practice guidelines while providing patients with clinically appropriate genetic testing **(Figure 4)** without increasing coverage denials due to

inappropriate filing or other administrative reasons **(Figure 6)**. Moreover, trends in decrease denials **(Figure 7)** can be attributed to education and QA measures, ensuring correct coding and medical necessity as described by medical policy.

Contact

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Guidelines and Recommendations

A. American Medical Association (AMA)

Within the 2020 AMA CPT guidelines concerning Genomic sequencing procedures and other molecular multianalyte assays, they state, "Genomic sequencing procedures (GSPs) and other molecular multianalyte assays GSPs are DNA or RNA sequence analysis methods that simultaneously assay multiple genes or genetic regions relevant to clinical situation. They may target specific combinations of genes or genetic material, or assay the exome or genome. The technology used for genomic sequencing is commonly referred to as next generation sequencing (NGS) or massively parallel sequencing (MPS). GSPs are performed on nucleic acids from germline or neoplastic samples. Examples of applications include aneuploidy analysis of cell-free circulating fetal DNA, gene panels for somatic alterations in neoplasms, and sequence analysis of the exome or genome to determine the cause of developmental delay. The exome and genome procedures are designed to evaluate the genetic material in totality or near totality. Although commonly used to identify sequence (base) changes, they can also be used to identify copy number, structural changes, and abnormal zygosity patterns. Another unique feature of the GSP's is the ability to "re-query" or re-evaluate the sequence data (eg, complex phenotype such as developmental delay is reassessed with new genetic knowledge is attained, or for a separate unrelated clinical indication) ... These codes should be used with the components of the descriptor(s) are fulfilled regardless of the technique used to provide the analysis, unless specifically noted in the code descriptor. When a GSP assay includes gene(s) that is listed in more than one code descriptor, the code for the most specific rest for the primary disorder sought should be reported, rather than reporting multiple codes for the same gene(s). When all of the components of the descriptor are not performed, use individual Tier 1 codes. Tier 2 codes, or 81479 (Unlisted molecular pathology procedure)[62]."

The AMA goes on to state that "[t]he assays in this section represent discrete genetic values, properties, or characteristics in which the measurement or analysis of each

analyte is potentially of independent medical significance or useful in medical management. In contrast to multianalyte assays with algorithmic analyses (MAAAs), the assays in this section do not represent algorithmically combined results to obtain a risk score or other value, which in itself represents a new and distinct medical property that is of independent medical significance relative to the individual, component test results[62]."

B. American Society of Clinical Oncology (ASCO)

The ASCO published a policy statement update in 2015 on genetic and genomic testing for cancer susceptibility that included recommendations for multi-gene panel testing for cancer susceptibility. ASCO recognizes that panel testing "may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient's personal or family history of cancer". ASCO notes that panel testing will identify variants of uncertain significance (VUSs) often, but that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility [63].

ASCO states that there is little consensus as to which genes should be on gene panels and that clinical utility is "the fundamental issue with respect to testing for mutations in moderate-penetrance genes". At this time (2015) there is insufficient evidence to "conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations" and that until these questions are answered, testing should be limited to mutations of established clinical utility [63].

C. American College of Medical Genetics (ACMG)

The ACMG published guidelines on inclusion criteria for genes with "various gene–disease evidence levels". For confirming a clinical diagnosis, the ACMG stated to include any gene associated (with a "moderate", "strong" or "definitive" association) with the disease, as long as the primary method of diagnosis was a "Disease-focused multigene panel or other non–sequencing-based ancillary assays". Genes with no emerging evidence or without evidence at all were to be excluded. Genes with emerging evidence should "typically" be excluded, although the ACMG notes some inclusions that may be "meaningful". The ACMG also states that genes with this level of evidence should be reported with a statement that disease association and inheritance has not been established.

For panels intended to "Establish genetic diagnosis for clinically complex cases" and that are used for conditions primarily diagnosed through exome/genome sequencing, genes that have evidence levels of "definitive", "strong" and "moderate" should be included. Genes of unknown significance should be qualified with a statement that disease association and inheritance have not been completely established [64].

The ACMG recommends that the selection of genes and transcripts in any given panel be limited to genes with "sufficient scientific evidence for a causative role in the disease".

Genes without clear evidence of association with the disease should not be included. ACMG recommends validating diagnostic testing through another method such as Sanger sequencing. ACMG cannot recommend a minimum threshold for "coverage" as many factors of the platform and assay may influence minimum coverage. However, the ACMG recommends that each laboratory independently validate their panel tests [55].

D. European Society of Human Genetics (ESHG) and EuroGentest

In 2016, the ESHG and EuroGentest co-published guidelines for the evaluation and validation of NGS for the diagnosis of genetic disorders in the *European Journal of Human Genetics*. Their guidelines and recommendations consisted of 38 overarching statements that included the following[65]:

- "NGS should not be transferred to clinical practice without an acceptable validation of the tests according to the emerging guidelines."
- "The laboratory has to make clear whether the test that is being offered may be used to exclude a diagnosis, or to confirm a diagnosis."
- "The aim and the utility of the test or assay should be discussed at the beginning of the validation and a summary should be included in the validation report."
- "For diagnostic purpose, only genes with a known (ie, published and confirmed) relationship between the aberrant genotype and the pathology should be included in the analysis."
- "For the sake of comparison, to avoid irresponsible testing, for the benefit of the patients, 'core disease gene lists' should be established by the clinical and laboratory experts."
- "The laboratory has to provide for each NGS test the following: the diseases it targets, the name of the genes tested, their reportable range, the analytical sensitivity and specificity, and, if possible, the diseases not relevant to the clinical phenotype that could be caused by mutations in the tested genes."
- "The report of a NGS assay should summarize the patient's identification and diagnosis, a brief description of the test, a summary of results, and the major findings on one page."
- "Data on UVs [Unknown Variants] have to be collected, with the aim to eventually classify these variants definitively."
- "A diagnostic test is any test directed toward answering a clinical question related to a medical condition of a patient."
- "A research test is hypothesis driven and the outcome may have limited clinical relevance for a patient enrolled in the project[65]."

E. Center for Medical Technology Policy (CMTP, 2015): Green Park Collaborative

In 2015, the Green Park Collaborative recommended that panels containing from 5 to 50 genes should be covered when the following criteria are met:

A subset of at least 5 constituent genes or variants is cited in the label of an FDA-approved companion diagnostic indicated for treatment, designated as standard of care for the underlying condition by molecular testing committees of at least 3 National Cancer Comprehensive Network (NCCN) member institutions, or recommended for decision-making for the underlying diagnosis in nationally recognized clinical guidelines, such as those of the NCCN or other guidelines that meet the IOM criteria for clinical guidelines.

OR

"The provider has submitted two peer-reviewed journal articles of studies designed to demonstrate the safety and effectiveness of using the genomic information in question for clinical management of the patient's diagnosis and support the conclusion that use of the information is reasonably likely to provide a health benefit for the patient."

AND, in all cases:

"The cost of analysis by NGS does not exceed the cost of individual sequencing of the target genes by other methods, AND the laboratory conducting the analysis is CLIA-certified and accredited by CAP for NGS testing [66].

The Collaborative proposed panels over 50 genes that "should be considered" for coverage if providers have sought prior authorization demonstrating the following diagnoses:

- Stage IV adenocarcinoma of the lung
- Carcinoma of unknown primary site
- Stage IV rare or uncommon solid tumors for whom no systemic treatment exists in clinical care guidelines and/or pathways;
- Stage IV solid tumors where the median overall survival is less than two years (such as pancreatic cancer)
- Stage IV solid tumors and has exhausted established guideline-driven systemic therapy options and requisite molecular testing and maintains functional status (ECOG score 0-2) OR
- newly diagnosed hematologic malignancies with limited treatment options in defined clinical care guidelines [66].

F. Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists (2017)

The Joint Commission recommended that somatic variants be categorized by and reported based on their impact on clinical care. The Joint Commission notes that somatic variants include indels, SNVs, fusion genes from genomic rearrangements, and CNVs and should focus on their impact on clinical care. Any variant may be considered a biomarker if it predicts response to therapy, influences prognosis, diagnosis, treatment decisions, or the gene function itself. The Joint Commission proposes four levels for these biomarkers which are as follows:

1. "Level A, biomarkers that predict response or resistance to US FDA-approved therapies for a specific type of tumor or have been included in professional guidelines as therapeutic, diagnostic, and/or prognostic biomarkers for specific types of tumors;

2. Level B, biomarkers that predict response or resistance to a therapy based on well-powered studies with consensus from experts in the field, or have diagnostic and/or prognostic significance of certain diseases based on well-powered studies with expert consensus;

3. Level C, biomarkers that predict response or resistance to therapies approved by FDA or professional societies for a different tumor type (ie, off-label use of a drug), serve as inclusion criteria for clinical trials, or have diagnostic and/or prognostic significance based on the results of multiple small studies;

4. Level D, biomarkers that show plausible therapeutic significance based on preclinical studies, or may assist disease diagnosis and/or prognosis themselves or along with other biomarkers based on small studies or multiple case reports with no consensus."

The Joint Commission also includes variants in different tiers based on the amount of evidence there is to support its significance. For example, tier 1 variants include significance of levels A and B and tier 2 includes significance of levels C and D. Tier 3 is variants of unknown significance (VUS), such as variants in cancer genes that haven't been reported in any other cancers. These variants are not typically seen in significant frequencies in the general population. When evaluating these variants, the type of mutation and gene function should be considered. Tier 4 is benign variants or likely benign variants. These alleles are often observed in significant amounts in general populations. Tier 3 variants should be reported while ensuring that the most important information is communicated to the patient [67].

G. National Comprehensive Cancer Network (NCCN)

The NCCN releases guidelines based on the type of cancers rather than by the methodology of screening. Within the Version 3.2020 Breast cancer guidelines, the NCCN recommends NGS alongside PCR and FISH for *NTRK* fusion testing. "Neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions are seen in of a few rare types of cancer, such as secretory carcinoma of the breast or salivary gland and infantile fibrosarcoma and also infrequently in some common cancers, such as melanoma, glioma, and carcinomas

of the thyroid, lung and colon. *NTRK* fusions are identified by fluorescence in situ hybridization (FISH), Next Generation Sequencing (NGS) or polymerase chain reaction (PCR). Larotrectinib and entrectinib are two NTRK-inhibitors that are U.S. FDA approved for the treatment of solid tumors that have an NTRK (*sic*) gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment. If patient with recurrent/stage IV breast cancer presents with a tumor with an *NTRK* fusion, treatment with a NTRK-inhibitor is an option if no satisfactory alternative treatments exists or that have progressed following treatment[22]." Concerning *BRCA* testing, the NCCN states, "Assess for germline *BRCA 1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP-inhibitor monotherapy. While olaparib and talazoparib are FDA indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline *BRCA1* or *BRCA2* mutation[22]." The NCCN also now recommends *BRCA 1/2* germline testing for individuals with triple-negative breast cancer (TNBC) for possible PARP-inhibitor monotherapy in addition to PD-L1 expression.

Federal/State Regulations

A. FDA

On November 30, 2017, the FDA approved FoundationOne CDx, by Foundation Medicine, Inc. This device is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens [68].

On June 29, 2017, the FDA approved Praxis Extended RAS Panel, by Illumina, Inc. The Praxis™ Extended RAS Panel is a qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples [69].

On June 22, 2017, the FDA approved Oncomine Dx Target Test, by Life Technologies Corporation. The Oncomine Dx Target Test is a qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM Dx System [70].

On December 19, 2016, the FDA approved FoundationFocus CDxBRCA, by Foundation Medicine, Inc. The FoundationFocus CDxBRCA is a next generation sequencing based in

vitro diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. The FoundationFocus CDxBRCA assay detects sequence alterations in BRCA1 and BRCA2 (BRCA1/2) gene [71].

A search of the FDA device database on 03/26/2020 for 'NGS' yielded 182 records. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

B. CMS

NCD 90.2 Next Generation Sequencing (NGS—Please note that the following is taken directly from the CMS website[72]).

A. General

Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, in vitro companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion in vitro diagnostic test.

Patients with cancer can have recurrent, relapsed, refractory, metastatic, and/or advanced stages III or IV of cancer. Clinical studies show that genetic variations in a patient's cancer can, in concert with clinical factors, predict how each individual responds to specific treatments.

In application, a report of results of a diagnostic laboratory test using NGS (i.e., information on the cancer's genetic variations) can contribute to predicting a patient's response to a given drug: good, bad, or none at all. Applications of NGS to predict a patient's response to treatment occurs ideally prior to initiation of such treatment.

Indications and Limitations of Coverage

B. Nationally Covered Indications

Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

1. Patient has:

either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and,

either not been previously tested using the same NGS test for the same primary diagnosis of cancer, or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and,

decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. The diagnostic laboratory test using NGS must have:

Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,

an FDA-approved or -cleared indication for use in that patient's cancer; and,

results provided to the treating physician for management of the patient using a report template to specify treatment options.

C. Nationally Non-Covered

Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1. above.

D. Other

Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of other NGS as a diagnostic laboratory test for patients with cancer only when the test is performed in a CLIA-certified laboratory, ordered by a treating physician, and the patient has:

either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and,

either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test was performed only when a new primary cancer diagnosis is made by the treating physician; and, decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

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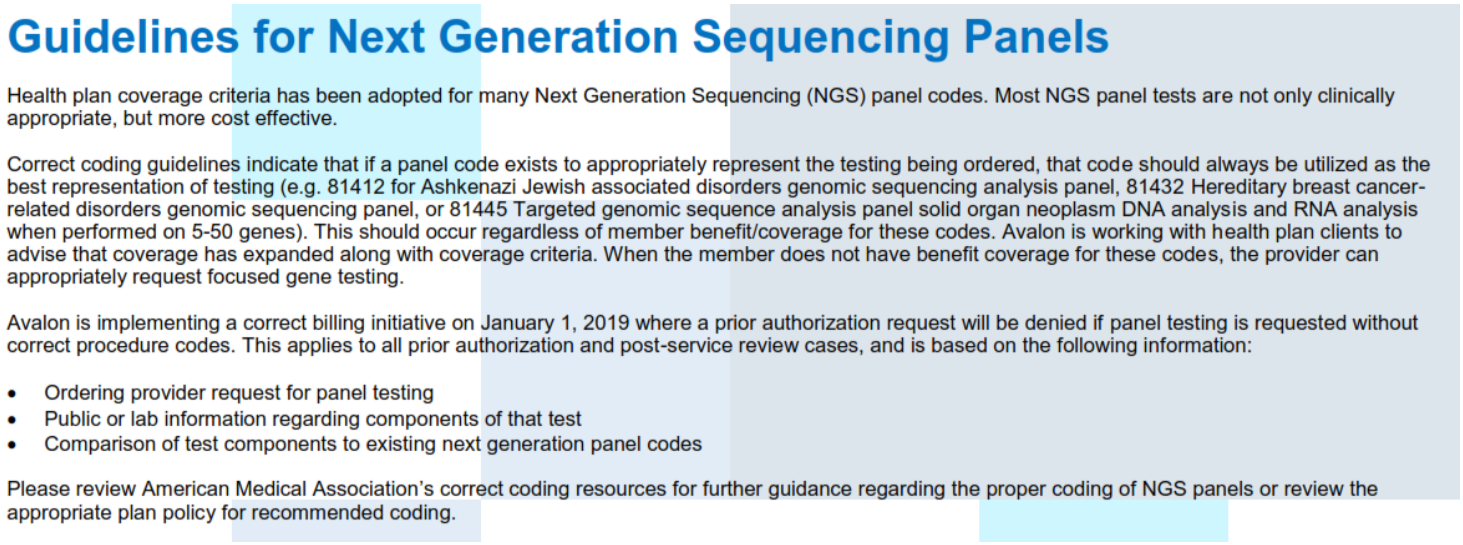
Supplemental Information

Supplemental Table 1: AMA CPT® Codes[61]

Code	Definition
81162	*BRCA1* (*BRCA1*, DNA repair associated), *BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81211	*BRCA1*, *BRCA2* (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in *BRCA1* (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81212	*BRCA1* (*BRCA1*, DNA repair associated), *BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81213	Uncommon duplication/deletion variants
81215	*BRCA1* (*BRCA1*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81217	*BRCA2* (*BRCA2*, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81222	*CFTR* (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including *BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11,* and *TP53*
81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for *BRCA1, BRCA2, MLH1, MSH2,* and *STK11*
81479	Unlisted molecular pathology procedure

Supplemental Figure 1



Guidelines for Next Generation Sequencing Panels

Health plan coverage criteria has been adopted for many Next Generation Sequencing (NGS) panel codes. Most NGS panel tests are not only clinically appropriate, but more cost effective.

Correct coding guidelines indicate that if a panel code exists to appropriately represent the testing being ordered, that code should always be utilized as the best representation of testing (e.g. 81412 for Ashkenazi Jewish associated disorders genomic sequencing analysis panel, 81432 Hereditary breast cancer-related disorders genomic sequencing panel, or 81445 Targeted genomic sequence analysis panel solid organ neoplasm DNA analysis and RNA analysis when performed on 5-50 genes). This should occur regardless of member benefit/coverage for these codes. Avalon is working with health plan clients to advise that coverage has expanded along with coverage criteria. When the member does not have benefit coverage for these codes, the provider can appropriately request focused gene testing.

Avalon is implementing a correct billing initiative on January 1, 2019 where a prior authorization request will be denied if panel testing is requested without correct procedure codes. This applies to all prior authorization and post-service review cases, and is based on the following information:

- Ordering provider request for panel testing
- Public or lab information regarding components of that test
- Comparison of test components to existing next generation panel codes

Please review American Medical Association's correct coding resources for further guidance regarding the proper coding of NGS panels or review the appropriate plan policy for recommended coding.

Supplemental Figure 1: *Example of Provider Educational Material.* This was created and distributed to providers to help educate them on the changing guidelines with respect to NGS panels. This is only one of the examples provided during the course of the study.