Association for Molecular Pathology

Promoting Clinical Practice, Translational Research, and Education in Molecular Pathology

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Proposal to address CPT coding for Genomic Sequencing Procedures
Association for Molecular Pathology Economic Affairs Committee
March 2013

Introduction

Advances in DNA sequencing technology, commonly referred to as Next Generation Sequencing (NGS) or Massively Parallel Sequencing (MPS), are allowing us to analyze the human genome in complex and diverse ways. Anticipating that current assays are only the vanguard of many yet-to-be-invented approaches for genomic evaluation, we propose using the more general term "genomic sequencing procedures" (GSP) to describe these current and future diagnostic uses. Applications of this technology are resulting in new clinical diagnostic procedures that have not been available before and are having a significant impact on the practice of medicine. Though the analyte is, technically, nucleic acid, the clinical utilities are broad and difficult to define because of the very nature of nucleic acids and the large amounts of data produced by these procedures, requiring significant bioinformatic analysis and interpretation to provide clinically useful information. This document attempts to formulate a CPT coding structure to address these complexities. This document is a result of a series of discussions within the AMP Economic Affairs Committee. It identifies certain unique concepts that pertain to these new technologies, enumeration of the different applications in clinical diagnostics, and how one might apply a CPT coding strategy for them in a manner consistent with existing CPT principles, terminology, and usage. Ultimately we believe the proposed coding strategy should pivot on the clinical questions addressed by the assays while being relatively platform agnostic in order to accommodate technical advances.

Considerations

Transparency. Key premises in the development of the molecular pathology procedure codes were that they be transparent, easy to understand, and easy to use, a goal we pursued in addressing GSP codes. Transparency and usability should make it relatively simple for payers to identify which services are provided and to make coverage decisions in a targeted fashion which does not inappropriately incorporate or discriminate against other distinct services as happened with the original molecular pathology procedure codes or 'stacking codes.' Laboratories and pathologists also benefit in being appropriately reimbursed for their services.

Clinical Utility. An implicit assumption in this discussion is that codes can only be assigned to tests that have some acknowledged clinical value. This key tenet of CPT coding is challenged by many GSPs which technically have the capability of generating vast amounts of data, not all of which is clinically useful, and only a small part of which may be clinically relevant at any one time. While the availability of previously inaccessible stores of genetic information holds promise for a future wave of personalized medicine, fiscal, as well as medical and ethical

considerations, would seem to require some restraint in evaluating genomic information irrelevant to the specific clinical situation at hand.

Unique features of GSPs. The molecular pathology procedure codes primarily address the assessment of a specific variant, exon, or multiple exon sequences of a single gene. In contrast, many of the GSPs are designed to assay multiple genes relevant to a clinical situation, simultaneously, either by targeting specific combinations of genes or by masking data from sequencing the exome or genome. Historically, the clinical questions addressed by an assay have been largely molded by technological constraints, i.e. genetic questions are typically approached through sequential inquiries of potential target genes. With GSPs the disorder-specific multiple gene sequencing assay can potentially be less expensive and offer faster turn around times than testing for each gene separately and sequentially. There are other applications of GSPs as with invasive aneuploidy testing of circulating fetal DNA.

Another feature of GSPs, depending on the breadth of the assay design, is the ability to re-evaluate the sequence data to address a secondary clinical question or questions without the need for additional technical sequencing work. A "re-query" could reflect an iterative test done to evaluate a complex phenotype, such as developmental delay, or a re-query could be done at a remote time point for a separate, unrelated clinical indication. In addition, new pathogenic variants are appearing regularly in the medical literature and GSPs can offer the opportunity to re-query these loci and potentially issue revised reports. Re-querying the data would include additional data analysis work and interpretation appropriate to the clinical scenario.

Laboratories currently offering disorder-specific GSPs have to combine or "code stack" from both Tier 1 and Tier 2 sets of codes in a way that loses transparency. The coding strategy outlined in this proposal aims to regain that transparency. Currently, there is one multi-gene sequence analysis code: 81280 - Long QT syndrome gene analysis (eg, KCNQ1, KCNQ2, SCN5A, KCNE1, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); full sequence analysis. The new GSP codes for disorder-specific multi-gene sequence analysis intend to recapitulate this example.

Challenges.
It is acknowledged that a laboratory's test menu, patient population, and business model may lead individual providers to adopt different technical approaches for perceived reasons of simplicity, assay uniformity and cost-effectiveness. For example, as the costs of high throughput sequencing continue to fall, some laboratories may choose to develop and maintain a single exome or whole genome assay and apply application-specific masks *in silico* during interpretation rather than maintain multiple GSP multi-gene assays for specific clinical questions. While not common yet, one can envision that laboratories opting to use exome or genome approaches might perform a single technical service, the data from which could be used to address more than one relevant clinical question, either simultaneously or at different clinical encounters.

We also recognize the desire by payers to know what disease genes were tested and that laboratories may have different groups of genes in their genomic sequencing assay. Therefore, trying to establish a "one size fits all" concept is problematic.

Genomic Sequencing Assays. GSPs are only beginning to be employed clinically and the full gamut of their capabilities is yet to be appreciated. Nonetheless, we can identify several examples of GSPs in current clinical use and we can anticipate other obvious applications in the near future. Like most molecular techniques, genomic sequencing can be performed on nucleic acids from a neoplasm, from a pathogen, or from germline samples. Certain applications are currently in more widespread use than others. Aneuploidy analysis of cell-free circulating fetal DNA, a non-invasive alternative to amniocentesis, is probably the GSP with the highest test volume in 2012. Another relatively common application of the GSP are the disorder-specific multi-gene sequencing assays, which are currently offered by over a dozen clinical laboratories. Several laboratories are offering multi-gene analysis of cancers and at least one lab is offering a clinical cancer exome. Other laboratories are using GSPs to perform assays that were previously performed using older technologies, such as clonality studies in lymphoma. Looking forward, one can anticipate likely applications of GSPs, such as RNA sequencing for oncology and assessment of the microbiome for chronic disorders. Below are the most prominent clinical uses of GSPs considered by the committee during the formulation of this proposal. These examples are delineated because they would seem to identify distinct categories of use. We anticipate that still other applications of NGS will emerge that may not be reflected in this listing.

Examples of Clinical Genomic Sequencing Assays

1. Aneuploidy detection in circulating cell-free fetal DNA (chromosome 21 only or 21, 18, and 13). Examples include Sequenom's Materni T21 plus, Natera's T21 test, and Ariosa's Harmony assay.
2. Disorder-specific multi-gene evaluations for heritable disorders. Obtaining this information by means of GSP versus Sanger sequencing may offer some technological advantages over conventional methodologies, but the clinical questions being addressed are unchanged and the genes being interrogated are currently coded by using Tier 1 and/or Tier 2 codes when tested for individually. Examples include X-linked Intellectual Disability, Ashkenazi Jewish Carrier Screen, and Mitochondrial Disorders which are currently offered at multiple clinical genetics laboratories.
3. Identification of rare genetic defects in individual patients using GSP. This is clinically relevant information (i.e. it is not research) and should be recognized by CPT. Examples include targeted "Mendeliome only" GSPs, whole exomes, and whole genomes which are currently offered at multiple clinical genetics laboratories.
4. Multi-gene evaluation of a neoplasm for diagnostic, prognostic, and/or therapeutic decision-making. Some laboratories have developed multiple organ-specific GSPs for oncology (eg, one for lung cancer, one for colorectal cancer, etc.) while other labs are deploying single, broader GSPs that are appropriate for multiple different cancer types. This type of GSP can identify potentially targetable pathways and mutations in specific

malignancies (i.e. actionable mutations). Critical to this use is an understanding of the molecular pathogenesis of those processes and their potential for informing the tumor diagnosis and classification, behavior and prognosis, and determination of optimal therapy, all elements that will necessarily be different for different tumor types.
A second emerging application of GSPs to tumor testing is the evaluation of multiple mutations in order to identify enrollment in relevant ongoing clinical oncology trials. Participation in such trials does provide a real treatment option for many cancer patients, and expanded testing for this purpose should be recognized as clinically indicated (i.e. it is not research). Examples of multi-gene sequencing assay for oncology applications include those offered by the Knight Laboratory, Genome Pathology Services at Washington University, and Foundation Medicine's Foundation One assay.

5. Clonality assessment in lymphoma. For example, Sequenta's LymphoSight assay.
6. Whole exome and whole genome analysis of a neoplasm. Depending on the depth of coverage, these assays can be used simultaneously to assess a broad or narrow multi-gene analysis for diagnostic, prognostic, or therapeutic decision-making and generate a "cytogenomic view" of the neoplasm, similar to what is currently generated by cytogenomic arrays as a separate assay. This is not currently in widespread clinical use, but a clinical cancer exome is offered by at least one laboratory.
7. Microbiome evaluations (define by disease process such as Crohns disease), not currently in clinical use.

Technology Overview

Next generation sequencing information is obtained through the comparison of multiple 'reads' of individual DNA strands from a sample. NGS is sometimes described as massively parallel sequencing because large numbers of reads, when aligned against one another, allow for the assessment of individual nucleotides for the presence of sequence variations, often at lower percentages than are found in the 50:50 distribution typically found in an individual where, at a given position, one nucleotide is provided from one parent and a second from the other. In addition to sequence information, the relative number of reads may be used to deduce aneuploidy in specific regions of the genome or across the whole genome.
The **human exome** is a subset of DNA sequence from the **human genome**. The exome contains the DNA sequence from regions in the genome which encode primarily proteins (genes). The human exome constitutes 1.5-2% of the information in the human genome. **Depth of coverage** in NGS studies refers to how frequently (on average) a given nucleotide is sampled in the multiple reads obtained. So 100X coverage means 100 'reads' containing the nucleotide of interest. For statistical reasons high depths of coverage are necessary to confidently predict the presence at a low percentage of sequence variants at a given position in a sample. Due to a variety of technical factors, some regions of the genome sequence more 'easily' and have higher depths of coverage than others. This may necessitate performing studies at higher depths of coverage than might appear to be necessary to obtain adequate sampling of target regions of interest. Depth of coverage is not necessarily a proxy for quality, and experienced laboratories with optimized chemistries and bioinformatics may be able to achieve high sensitivity and specificity with lower coverage.

Technical work: Technical analysis varies according to rational design of assays for particular clinical questions, but virtually always involves multiple genes, regions within genes, and/or regions outside of genes. The breadth of sequence desired (several genes, many genes, the exome, the genome) and the depth of coverage (typically lower for heritable conditions or higher for neoplastic ones) drives which platform is chosen, how much data is collected, and how many samples can be run together (using molecular 'bar-coding') simultaneously to yield efficiencies. Different questions may require smaller or larger amounts of data, and as the understanding of the molecular pathology of a given question evolves, the optimal amount of data may grow, or shrink, depending on a revised understanding of which targets need to be sampled. There are substantial bioinformatics resources required to reliably convert bases to bytes and it cannot be done "manually"—bioinformatics in the technical component of GSP is a *sine qua non* and needs to be considered in the technical valuation of these assays. Because platforms which can interrogate multiple regions simultaneously will require data storage and bioinformatics skills not typically available in most clinical laboratories and which may be quite expensive, aggregation of samples may offer considerable efficiencies of scale. This leads some to predict that increasing amounts of GSP exome and genome technical work will be performed by large laboratories on out-sourced samples from sites which will choose to interpret this data in the context of their individual patients.

Professional work: Interpretation of sequence information from Sanger, next generation sequencing, or other technologies, must be done by highly trained professionals. Current DNA sequence data from 'traditional' (Sanger) methods must be carefully reviewed and evaluated by a laboratory professional with in-depth experience and training to provide an accurate assessment of nucleotide sequence variations present (benign and pathogenic), and to report these using standard nomenclature so meaningful clinical comparisons can be drawn from mutation databases and literature citations. Where the application of GSP s differs from traditional testing capabilities is the ability to simultaneously test diverse genes relevant to a particular neoplastic process or genetic disorder. In multi-gene sequencing studies, the amount and complexity of data is typically considerably greater than that from traditional targeted Sanger assays for individual genes. It should be appreciated that some disorders may require significantly more evaluation of the data with regards to understanding the molecular pathogenesis of those processes and their potential for informing patient management. Additionally, some are beginning to utilize GSP data to interpret copy number and structural changes which are currently interrogated using other assay methods. Consequently, we anticipate that the professional interpretative work in addressing the clinical questions may vary depending on the disorder, tumor type, or testing goal, even though the technical work involved may be very similar.

Proposed scheme for coding GSPs

Strategy

The technical and analytical work involved is potentially distilled into levels from least to greatest amount of work; targeted multiple gene sequencing, then exome sequencing, followed

by genome sequencing. The descriptor should provide a clear indication of the clinical question that is to be addressed by the assay (e.g. molecular changes to make a diagnosis or inform a therapeutic plan). The examples below are only a few potential codes that could be written for current assays. Needless to say the number of codes defining clinical questions will increase over time as benefits are demonstrated for multi-gene analysis in various circumstances. Smart coding strategies would likely benefit from, and indeed will likely require, input from panels of appropriate medical experts. The codes will encompass the technical or professional effort required to generate and interpret the data to provide an actionable answer to the requesting healthcare provider. These codes should be reviewed periodically to assess whether the definitions of the clinical question need to be narrowed or broadened based on experience and new knowledge.

In this model, a laboratory could write an X-linked intellectual disability report, for example, and the code is constant regardless of whether they did Sanger sequencing of 91 genes, targeted NGS, whole exome, or whole genome sequencing for the technical component. In circumstances where iterative genetic testing is likely (eg, intellectual disability) it may be more cost-effective to validate and maintain a single broad assay such as an exome or genome assay rather than multiple disorder-specific GSPs. In addition to laboratory management issues, the potential advantages of a single, broad GSP in certain iterative testing scenarios include lower overall genetic testing cost and faster turn around times for tests ordered iteratively. Based on patient population and laboratory management choices, each lab would decide which is the most appropriate and cost-effective technical strategy.

Hierarchical structure:

Multiple Gene/Genetic Region Genomic Sequence Analysis

GSAX1 X-linked intellectual disability (eg, *ABCD1, ACSL4, AFF2, AGTR2, AP1S2, ARHGEF6, ARHGEF9, ARX, ATP6AP2, ATP7A, ATRX, BCOR, BRWD3, CASK, CDKL5, CUL4B, DCX, DKC1, DLG3, DMD, FANCB, FGD1, FLNA, FMR1, FTSJ1, GDI1, GK, GPC3, GRIA3, HCCS, HPRT, HSD17B10, HUWE1, IDS, IGBP1, IL1RAPL, JARID1C, KIAA2022, KLF8, L1CAM, LAMP2, MAGT1, MAOA, MBTPS2, MECP2, MED12, MID1, MTM1, NDP, NDUFA1, NHS, NLGN3, NLGN4, NSDHL, NXF5, OCRL, OFD1, OPHN1, OTC, PAK3, PCDH19, PDHA1, PGK1, PHF6, PHF8, PLP1, PORCN, PRPS1, PQBP1, RAB39B, RPL10, RPS6KA3, SHROOM4, SLC9A6, SLC16A2, SMC1A, SMS, SOX3, SRPX2, SYN1, SYP, TIMM8A, TM4SF2, UBE2A, UPF3B, ZDHHC9, ZDHHC15, ZNF41, ZNF81, ZNF711*) genomic sequence analysis

GSAX2 Report and interpretation

GSAX3 Aortic dysfunction or dilation (eg, *FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, MYLK, FBN2*) (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome), genomic sequence analysis

GSAX4 Report and interpretation

GSAX5 Nonsyndromic hearing loss (eg, *CDH23, CLDN14, COL11A2, ESPN, ESSRB, GIPC3,GJB2, GJB3, GJB6, GPSM2, GRXCR1, HGF, ILDR1, LHFPL5, LOXHD1, LRTOMT, MARVELD2, MYO3A, MYO6, MYO7A, MYO15A, OTOA, OTOF, PCDH15, PJVK, PTPRQ, RDX, SLC26A4, SLC26A5, STRC,TECTA, TMC1, TMIE, TMPRSS3, TPRN, TRIOBP,USH1C, WHRN, ACTG1, CCDC50, COCH, COL11A2, CRYM, DFNA5, DIAPH1, DSPP, EYA4, GJB2, GJB3, GJB6, GRHL2, KCNQ4, MYH14, MYH9, MYO1A, MYO6, MYO7A, POU4F3, SLC17A3, TECTA, TMC1, TJP2, WFS1, POU3F4, PRPS1*), genomic sequence analysis

GSAX6 Report and interpretation

Quantitative Genomic Sequence Analysis

QGSAX1 Fetal chromosomal anueploidy (eg, chromosome 13, 18, 21) (eg, trisomy 21, trisomy 18 and trisomy 13) from circulating cell-free fetal DNA, genomic sequence analysis

QGSAX2 Report and interpretation

Exome Genomic Sequence Analysis

GSAX90 Exome (eg. Unexplained constitutional or heritable disorder or syndrome) genomic sequence analysis

GSAX91 Re-analysis for unrelated condition or syndrome

GSAX92 Report and interpretation

Genome Genomic Sequence Analysis

GSAX96 Genome (eg, unexplained constitutional or heritable disorder or syndrome) genomic sequence analysis

GSAX97 Re-analysis for unrelated condition or syndrome

GSAX98 Report and interpretation

In keeping with the principles that guided the development of the new molecular pathology procedure codes, our committee believed that a single, methodology-agnostic code,

encompassing both technical and interpretive work could potentially be ascribed to certain GSP assays. However, we considered separate, indication-specific technical and clinical interpretation "code mates," useful in distinguishing the separate and distinct importance of the clinical question, and, inherently, the professional interpretive work from the technical work.

Additional advantages of the "code mate" approach include:

a) It will be clear to payers who provided technical and interpretive services when these are conducted by separate entities.
b) This approach could easily accommodate re-evaluation of existing data to address new clinical questions, perhaps pairing a modified technical code with a new clinical code.
c) Technical codes can be revised and /or revalued as technological advances occur.

This distinction is also important in situations that call for reiterative evaluation of previously determined data, where the major technical work is accomplished once, but a sequential inquiry is needed to address a second focused clinical question.

The possible disadvantages of the "code mate" approach include:

a) It is inconsistent with the single unit of service which is desired by the payers
b) In settings where iterative genetic testing may be required (eg, developmental delay, hereditary neuropathies), it could de-incentivize laboratories to develop testing strategies that may cost less and provide a faster turn-around-time due to the "test once, repeat query" option of broad-based GSP assays such as whole exome and whole genome.

Harmonization with Molecular Pathology Procedure Codes. What if a code already exists on Tier 1 or Tier 2 for one, some, or all of the genes targeted in a disorder-specific multi-gene assay? Which code is used depends on what the ordering physician requested. If the doctor ordered a CF "whole gene sequence analysis", then one would write a report for CF whole gene and use the Tier 1 code for CF whole gene sequence analysis (81223 CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystis fibrosis) gene analysis; full gene sequence), regardless of the technical method used. If the order is for an Ashkenazi Jewish Carrier panel, which happens to include CF, then one reports for an AK Carrier Panel and uses the new AK Carrier Multi-gene code. The code used depends on the report written, not on the technique used or how much other data may or may not have been generated. Likewise, if a laboratory is performing genome or exome sequencing and has validated the assay for "cytogenomic" use, they could write a "cytogenomic" report and use the existing cytogenomic array codes. In keeping with the method-agnostic philosophy of the molecular pathology procedure codes, we do not feel that cytogenomic reports generated from GPAs warrant a method-specific code.

Summary

This proposal describes a framework for the development of CPT codes to be used for assays that utilize novel sequencing technologies, collectively referred to as Genomic Sequencing Procedures (GSPs). These assays encompass what are commonly referred to as Next Gen

sequencing assays but are not limited to that technology, anticipating that even these will be supplanted by technologies and methodologies still in development. In this proposal we sought to adhere to the basic tenet of CPT that any recognized test should have some established clinical utility. We also sought to adhere to basic principles of transparency and clarity necessary for the practical use of these codes. A further constraint was that the new scheme be agnostic to any particular platform or technology assuring its applicability well into the future.

With those underlying principles in mind, we sought to consider the unique features of GSPs that distinguish them from current technologies, and subsequently endeavored to understand how these assays are, and can be, used clinically. In consideration of both of these elements a scheme for coding was developed that is coherent with general CPT principles, the desire for transparency, is in harmony with the existing Molecular Pathology Procedure codes, and which provides a mechanism to establish new codes that explicitly recognize truly novel clinical tests that could not be recognized by the existing codes.
With consideration of the unique kinds of information that GSPs can provide and the unique clinical questions that can now be addressed, we believe that this proposal can allow for appropriate new codes to be devised and defined. This proposal is not intended to address all the nuances that must necessarily accompany any novel technology or endeavor, particularly one as momentous as that brought about by our new found abilities to interrogate the human genome, but we do intend that this proposal serve as a solid framework for further discussion and development by interested parties, and hope that our discussions and deliberations serve to inform, advance, and inspire those efforts.

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