BRUCE QUINN ASSOCIATES LLC

HEALTH INNOVATION MADE REAL.

Cancer Patients and Access to Molecular Diagnostics

Understanding the Transition Toward Comprehensive Genomic Profiling and Tumor Mutation Burden Testing

Bruce Quinn Associates LLC
LOS ANGELES | SAN FRANCISCO

April 2022

About Bruce Quinn, MD, PhD

Dr. Quinn brings twenty years of real-world experience in healthcare and twelve years of corporate consulting experience to your problem.

Education

- MD-PhD at Stanford University
- Postdoctoral fellow, neuroscience, MIT
- Residency, pathology and neuropathology, UCLA
- MBA, Kellogg Graduate School of Management

Experience

- Bruce Quinn Associates, Los Angeles and Palo Alto (Principal)
- FaegreBD Consulting, Washington and Palo Alto (Policy & Strategy Expert), 2015-2016
- Foley Hoag LLP, Boston and Washington (Policy & Strategy Expert), 2008-2015
- Medicare Program, California (Medical Director), 2004-2008
- Accenture, Chicago and Los Angeles (Physician Executive), 2001-2004
- Northwestern University School of Medicine (Faculty), 1997-2001
- Bellevue City Hospital and NYU School of Medicine (Faculty), 1994-1997

RICHARDCODA DESIGN LLC Graphic Design by Richard Coda
www.richardcodadesign.com

Contents

Executive Summary

Tumor tissue can be sequenced to inform the best choice for cancer therapy. 2013 saw the first FDA approvals of single-gene EGFR tests, the QIAGEN therascreen® EGFR and the Roche cobas® EGFR Mutation tests (FDA 2013b; FDA 2013a). From that beginning, and in less than 10 years, the range and diversity of genomic tests for cancer patients has skyrocketed (FDA 2021b). FDA has now approved single assays with as many as 324 genes measured simultaneously on a single sophisticated platform (the FoundationOne CDx test, (FDA 2020b)).

Gene-by-gene analysis with separate tests is cumbersome, and becomes costly when each gene is reported and priced as separate line item. The new standard is coming to be "comprehensive genomic profiling," or CGP. Several factors are driving this. First, for single cancers, there are more and more targeted therapies, each paired to a different gene or genomic feature. All of these on-label genes can be incorporated in CGP panels. Second, some newly-important genes have very low prevalence (including ALK, ROS1, and NTRK1,2,3), so testing them one at a time outside of CGP would be impractical. Third, there are many types of oncology mutations, some of which aren't easily detected by older sequencing method. CGP tests using next-generation sequencing assess a range of different mutations in one assay including point mutations, small and large insertion-deletions, rearrangements or oncogene fusions, and large copy number duplications and losses (Boyle et al. 2021).

Guidelines from the National Comprehensive Cancer Network (NCCN) endorse use of CGP, as do new guidance from the American Society of Clinical Oncology (ASCO) (Chakravarty et al. 2022). The most recent publication on clinical utility of genomic testing from the Personalized Medicine Coalition (PMC) also focuses on the value of CGP (Pritchard et al. 2022). And packaging these genetic tests together in one assay has also been shown to be a wise choice from the viewpoint of health economics (Chawla et al. 2018; Pennell 2019; Johnston et al. 2020; Harvey et al. 2021; Patel et al. 2021).

Two additional features of CGP are important. CGP can assess micro-satellite instability (MSI) and tumor mutation burden (TMB), both of which are important biomarkers for immune-oncology drugs (such as checkpoint inhibitors). In this area, Keytruda (pembrolizumab), was approved by the FDA in June 2020 for use in advanced solid cancers with high tumor mutation burden (TMB); (FDA 2020a). TMB analysis is based on sequencing of 1.5 mb or more of the tumor's DNA. While this sequencing can be conducted as part of a whole-exome analysis, today TMB assessments are most often conducted as a part of CGP, providing another FDA-based rationale for CGP testing.

For patients on Medicare, FDA-approved genomic testing of tumors is covered, and includes TMB testing. Medicare established this coverage in February 2018 through a National Coverage Determination for FDA-approved, NGS-based oncology panel tests (CMS 2021).

However, in 2020 and 2021, policy experts have reported lagging coverage for CGP testing in some sectors of the insurance marketplace (Hsiao et al. 2020; Trosman et al. 2020; Hopkins 2021b).

In this white paper, we discuss how the current reimbursement system for tumor genomics evolved. We discuss these findings in light of the new need to cover assessment of TMB and as well as less-common genes (the "long tail") to support the management of cancer patients.

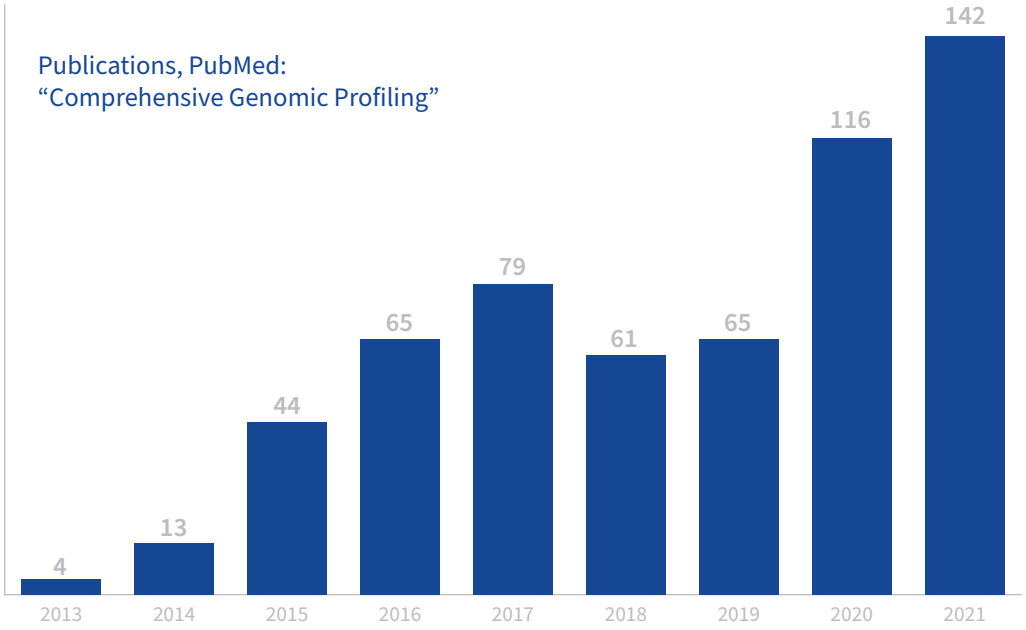
1

Understanding Comprehensive Genomic Profiling (CGP)

Understanding Comprehensive Genomic Profiling (CGP)

Comprehensive genomic profiling, or CGP, are assays that use Next Generation Sequencing technology to reveal a spectrum of somatic genetic changes that drive the proliferation of cancer. These changes are not fixed – they actively evolve during treatment to make the cancer therapy-resistant (Labrie et al. 2022).

The term **CGP** has risen steadily in use since introduced in 2013, and is now being cited in over 100 oncology publications per year:



The American Medical Association defines tumor profiling as:

> **Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, with interrogation for sequence variants and copy number variants or rearrangements, if performed.**

The Medicare program has a definition of tumor profiling that distinguishes targeted or "hot spot" testing from broad genomic testing or large areas of DNA, which is to say, CGP. MolDx, the Medicare system of four Medicare contractors spanning 28 states, has two policies for comprehensive genomic profiling, one for solid tumors and one for myeloid cancers. In MolDx policy L38045, they carefully distinguish true CGP from "hot spot" tests that sample a much smaller number of genomic abnormalities. Per MolDx Policy L38045, CGP tests will generally be able to report all the following:

- Single nucleotide variations
- Small insertion-deletions, or Indels (typically less than 20 base pairs)
- Larger indels
- Copy number variation, e.g. gene duplication or loss
- Gene fusions or translocations
- MolDx states that CGP tests can be used to:
- Calculate of microsatellite instability status, which reflects a lack of DNA repair enzymes
- Calculate tumor mutation burden, which represents quantity of abnormal genes resulting in abnormal proteins the immune system can attack

Illumina, which sponsored this independent white paper, also provides a website describing comprehensive genomic profiling (Illumina 2021). On state-of-the-art high-volume sequencing platforms, up to 70 tumors can be run concurrently on a 500-gene test with a 7-day turnaround time (Conroy et al. 2021).

The Evolution from Simple to Complex Genomic Tests

Modern precision oncology began with the FDA approval of Herceptin (trastazumab) in 1998 (Bazell 1998; Wikipedia 2021). Herceptin is a monoclonal antibody therapy designed to treat breast cancers that overexpress a growth protein called her2-neu. This biomarker was detected by proteomic testing (immunohistochemistry), but since then, the great majority of biomarkers are genomic ones (Jorgensen 2013; Hanamura and Aruga 2014; Verma 2014; Dracopoli and Boguski 2017; Jorgensen and Hersom 2018). This pivot to genomic testing is grounded in the modern understanding that cancer is a "genomic disease" (Greenman et al. 2007; Stratton et al. 2009; Berger and Mardis 2018).

In an analysis through 2017, there were 150 approved anti-cancer drugs at the FDA, and 89 of them were classified as targeted drugs (Baldo and Pham 2020). The target drugs generally have FDA-approved genetic tests. In terms of specific technologies, the FDA has approved either single-gene tests, or approved relatively large panels that carry from 23 to over 300 genes. Examples range from the 23-gene Oncomine CDx test to the the 384-gene FoundationOne CDx test (Allegretti et al. 2018).]

Turning to lab-developed tests, we focus on large tests that meet the Medicare and AMA definitions of comprehensive genomic profiling, such as the Caris test, which sequences at a depth of 1000X for 720 genes (Caris 2021), Omniseq INSIGHT, which assesses 523 genes (OmniSeq 2021), and the Columbia Combined Cancer Panel (CCCP), which tests 467 genes (Hsiao et al. 2020). Boyle et al. at Moffitt Cancer Center have validated a 170-gene test (Boyle et al. 2021). Tests reviewed and passed by the FDA under the 510(k), rather than companion diagnostic, process have also been comprehensive genomic profiling tests, such as the PGDx elio™ test, which assesses 505 genes (FDA 2020c) and the Memorial Sloan Kettering "IMPACT" test assessing 468 genes (FDA 2017).

Large Genomic Panels (CGP)

Representative CGP Test	Gene Count	FDA Status	Distributed?
Caris	720	Pending	No
OmniSeq INSIGHT	523	No	No
PDGx Elio	505	Yes – 510k cleared	Yes
Illumina TruSight Oncology 500	523	No	Yes
Illumina TruSight Oncology Comprehensive	Pending	Pending	(Pending)
Sloan Kettering MSK-IMPACT	468	Yes- 510k cleared	No
Columbia Combined Cancer Panel	465	No	No
Foundation Medicine F1CDx	384	Yes – PMA approved	No
Moffitt STAR Solid Tumor Assay	170	No	No

Studies Report the Value of CGP

The value and clinical uses of CGP have been studied in many publications in recent years. For example, Cobain et al. (Cobain et al. 2021) in Ann Arbor reported on use of CGP in 1015 patients over a 7-year period at one large academic center. 80% of patients (817/1015) had potentially actionable patients, and moreover, successful NGS results were obtained in 90% (1015/1138) of patients where NGS CGP testing was ordered. Overall, 16% of patients received sequencing-directed therapy. This reflects the fact, as recently explained well by Adashek et al., that even in 2021, a majority of cancer patients do not have cancers with targeted therapy mutations (such as EGFR or ALK), and the only way to identify the critically important population of those who do, is via CGP sequencing (Adashek et al. 2021).

Pennel and colleagues looked at the clinical and economic impact of gene panel testing (Pennell 2019). They modeled a 1M person population, in which 2,066 Medicare and 15 commercial patients would be diagnosed with advanced-stage lung cancer and eligible for CGP testing. NGS panel testing was more economically efficient than either sequential or hot-spot testing (saving $127,000 and $250,000, respectively.) Chawla et al. also found that the results of NGS testing were economically neutral to favorable (Chawla et al. 2018). Patel reporting CGP in lung cancer as having a value of $88,000/QALY using the liquid biopsy modality (Patel et al. 2021). Harvey et al. found that CGP testing in lung cancer improved outcomes and had a modest budget impact, part of which was attributed to longer survival (Harvey et al. 2021).

Hsiao and colleagues at Columbia studied a 467-gene panel in 249 patients, finding clinically impactful findings in 229 cases (64%) (Hsiao et al. 2020). Importantly, these authors report that 80% of targeted alterations would not have been detected by a previously available 50-gene hotspot panel. 18% received a targeted therapy. Another form of benefit, reflecting in the 100-plus publications per year on CGP, is that we are accumulating far more knowledge about many less-common or rare cancers such as urethral carinomas and neuroendocrine carcinomas (Jacob et al. 2021; Lu et al. 2021; Yachida et al. 2022).

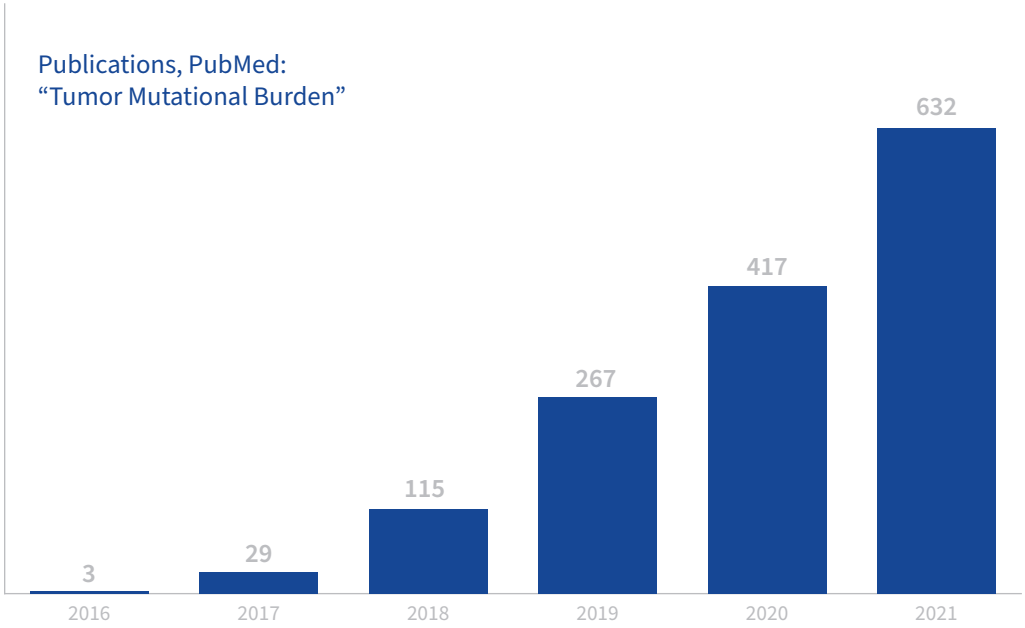
Taken together, these publications support a strategy where NGS technologies become increasingly efficient at broader scale in oncology, just as we see in other areas of molecular medicine (Varesio et al. 2021).

2

Understanding Tumor Mutation Burden (TMB)

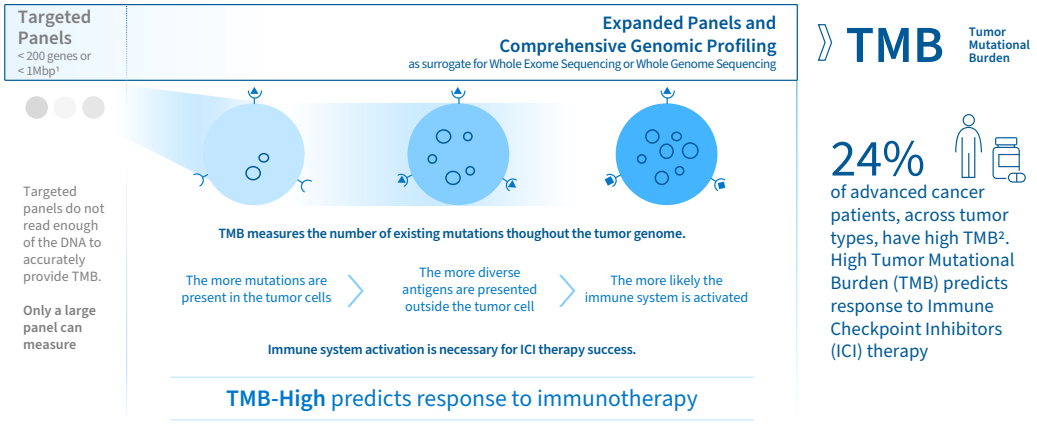
Understanding Tumor Mutation Burden (TMB)

Basic science and clinical research on tumor mutation burden (TMB) has truly boomed in the last several years:



This growth reflects the importance of TMB as a biomarker that can guide choices of immuno-oncology therapy in a range of cancers. Progress has been exponential since initial reports calculating TMB using sequencing data from the Foundation Medicine (Ashford 2016). For up-to-date TMB review publications, see (Gautam et al. 2021; Kim et al. 2021; O'Meara and Tolaney 2021; Sung et al. 2021; Wagener-Ryczek and Buettner 2021; Cristescu et al. 2022; Du and Liu 2022; Meng et al. 2022; Wang et al. 2022).

A key fact driving TMB reporting has been the discovery that some kinds of cancer accumulate far more scattered mutations – their mutation burden – than others. Even with cancers of the same type, the TMB burden may vary considerably from one patient to another. Sometimes, the cause of the mutation burden is apparent, such as in patient with high mismatch repair enzyme defects that cause high microsatellite instability (MMR and MSI, respectively). However, more cancers have high TMB than have defects in MMR and high MSI, making TMB an independent genomic marker that is separate from MMR/MSI.



1 Buchhalter I, Rempel E, Endris V, et al. Size matters: Dissecting key parameters for panel-based tumor mutational burden analysis. *Int J Cancer*. 2019;144(4):848-858. doi:10.1002/ijc.31878
2 Critescu R. et al. *AACR Annual Meeting* (2020) poster LB-261

TMB can be measured with large panel tests (e.g. panels with 200-300 genes and up) as well as using data from tumor exome sequencing. Multiple papers have converged on the finding that around 1.5MB of DNA (or more) should be measured to ensure statistically robust calculation of TMB. See for example (Chaudhary et al. 2018; Endris et al. 2019; Fancello et al. 2019; Pinato et al. 2020).

Several groups are actively working on harmonization and standardization initiatives for TMB (Stenzinger et al. 2019; Merino et al. 2020). While exome TMB measurement has been sometimes considered a "gold standard," recent papers find that TMB on large panels correlate effectively with exome-based TMB. One author has suggested targeted parts of the exome for TMB measurement (Guo et al. 2020), rather than either the whole exome or large oncogene panels.

One of the thorniest questions has been the relative role of PDL1 measurement in tumor tissue versus measurement of TMB. Much effort has gone into research on this topic (Looney et al. 2020; Dong et al. 2021; Doroshow et al. 2021; Twomey and Zhang 2021) but a consensus appears to be emerging that on the whole, TMB appears to be more predictive of responses to checkpoint inhibitor (immune-oncology) drugs than PDL1 measurement (Fabrizio et al. 2018; Vanderwalde et al. 2018; Schrock et al. 2019); see also (Du and Liu 2022; Palmeri et al. 2022; Wang et al. 2022). The clinical situation is proving important, so that TMB may be a more effective predictor in some tumor types than others, or different cut-offs for TMB will fit different tumor types. For more on these topics, see (McGrail et al. 2021; Rousseau et al. 2021). See also a review, by FDA authors, on the general challenges posted when developing strong biomarkers for immune-oncology drugs, whether that biomarker is TMB, PDL1 biomarkers, or other biomarkers (Li et al. 2020).

FDA Approval for TMB as a Companion Diagnostic

The landmark FDA approval for TMB was for use of pembrolizumab (Keytruda) in an advanced solid cancer for patients without other treatment options (FDA 2020a; FDA 2021b; FDA 2021a). The FDA landed on a 10 mb/megabase mutation rate as a cutpoint for a positive TMB call. The interesting story behind this approval, told from an FDA perspective, was recently published by Marcus et al. (Marcus et al. 2021). The FDA decision was based most strongly on the Keynote-158 study as reported in Lancet Oncology (Marabelle et al. 2020).

This page intentionally left blank for printing.

3

The Coding and Reimbursement System for CGP and TMB

The Coding and Reimbursement System for CGP and TMB

So far, we've reviewed the evolution of clinical testing for tumor genes, and the growing use of TMB testing, especially in immuno-oncology. Now we turn to a different aspect – the coding and payment systems for cancer tests.

Since the last genomics coding reform in 2013, much has been written about the complexities and frustrations of the U.S. reimbursement system for genomics (Lennerz et al. 2016; Hsiao et al. 2018; Quinn 2018; Trosman et al. 2018; Hopkins 2021b; Scheuner et al. 2021). Even basic terminology can be confusing among different types of stakeholders (LUNGevity 2020). The AMA held an all-day workshop in July 2021 about the level of dissatisfaction with where we've ended up, and potential directions for a new round of improvements (AMA 2021).

Let's take a trip to the past for a brief history of genetic coding. Prior to 2013, there were only a few codes for genetic tests, and they represented non-specific laboratory steps, such as "DNA extraction" and "DNA amplification."

> *For example, prior to 2013, analysis of a complex gene, with multiple exomes and amplification zones with exomes might have been coded as, "Amplification x 20." And it would have paid about $20 per step, or 20x$20, $400.*

In 2013, the American Medical Association, which controls the laboratory and physician office coding system, developed a new system which comprises a mix of single gene codes (such as sequencing the EGFR gene) and panel codes. The latter codes were given a new category heading, as "genomic sequencing procedures" or GSPs.

In 2013/2014, AMA introduced some 200 new codes, and phased them in over two years. There were just three codes for tumor panels (also known as somatic mutation panels). These three codes were:

- **Code 81445,** for solid cancer tumor panels of 5-50 genes,
- **Code 81450,** for hematopoietic cancer panels of 5-50 genes, and,
- **Code 81455,** for all cancer panels of 51 or more genes.

There have been minimal updates to these codes in the following from 2013 to 2022. Each of the codes currently states it is for tumor-based DNA analysis, and includes RNA analysis if performed. The code for "51 or more" genes, which would include CGP assays usually with 300-500 genes, is silent as to whether analysis of TMB or MSI/MMR is included. As of Autumn 2021, there are proposals to revise these codes but, if revisions occur, they will take effect in January 2023 at the earliest.

That's the background. What happens next? **First,** we will discuss some irrational economics that emerged from these 2013 codes as-written (and as preserved today 8 years later). **Second**, we will discuss some issues that will be important if we are entering an update cycle for these codes.

Reimbursement Economics Were Contradictory

In hindsight, there were several irrational aspects of these codes, and as a result, the way they were priced by Medicare became dysfunctional. This was important, because Medicare fee schedules are a sort of national reference standard for lab test prices at many payors.

First, when initially pricing the codes for "5 to 50 genes," CMS policy staff assigned the lowest possible price, for the minimum case of five genes. They calculated a price representing about $120 for each of the minimum five genes, totaling $600. The immediate consequence was that if a panel with five genes was fairly priced at $600, a panel ten times larger with 50 genes would be underpriced. But that's not all.

Labs immediately discovered that CMS would often pay more for some combinations of 2, 3, or up to 4 genes – as long as you didn't sequence "5" genes and trigger the "5-50" gene code. Let's see some examples.

- CMS initially priced BRCA sequencing at over $2000 for two genes.
  - —But if those two genes were included in a panel of ten genes, the payment fell to $600. (Crazy!)
- EGFR and KRAS gene analysis, coded with three codes (81235, 81275, 81276) pays $710, more than the code for 5 to 50 genes. 3 genes pay more than 50 genes.
- Full sequencing of just one Lynch syndrome gene, Msh6, coded for sequence and for dup del variants, pays $879 (code 81298 + 81300). This is a higher payment than is offered for the code 81445 for 5-50 genes, $600.
- In short, a coding and reimbursement system was produced that strongly incented labs to test 2-4 genes, rather than 5 to 50.

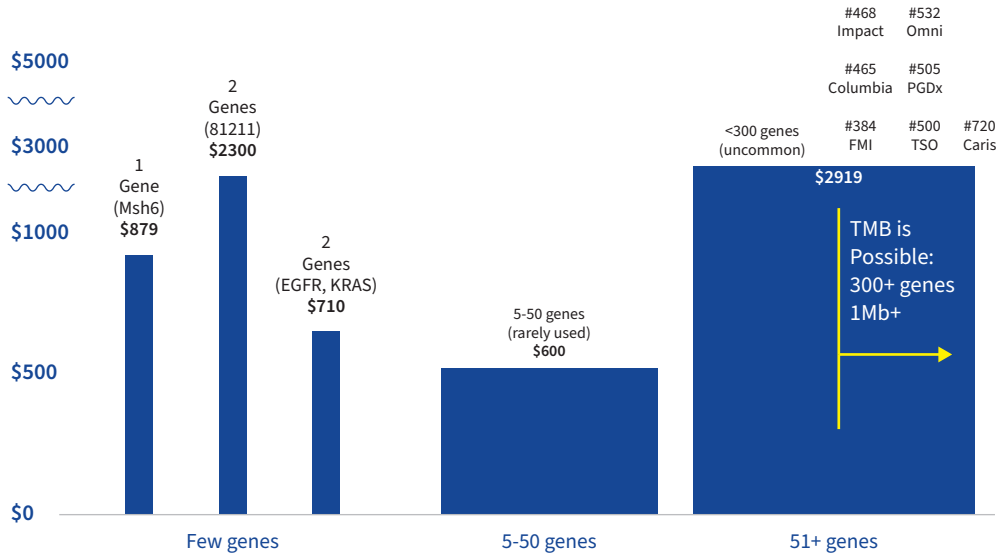
Let's turn to the coding of larger panels. In 2018, the tumor panel code 81455 was priced at $2919. This means if you test 50 genes, the price is $600 (code 81445), but if you add one gene more and report 51 genes, the price jumps to $2919 (code 81455).

Code 81455 and price $2919 represents any test of 51+ genes, but the Foundation Medicine FoundationOne CDx test held a large market share and set an anchor point for tests of this type. It fit the code for "51 or more genes" – having over 300 genes. Other tests entered the market with 300-500 genes as well.

If you put on your lab economist hat, you might have expected labs to produce tests at around 51 genes, since they get paid $2919 for 51 genes don't get paid any more for adding genes after the 51st gene. But test offerings did not aggregate around the 50-60 gene point.

Assuming lab test providers responded rationally to incentives related to both the fee schedule and to the marketplace, I'm inferring there was a lack of market demand for tests in the 50-100 gene range. For one thing, from 2016 or 2017 forward, it was becoming clear that larger DNA runs would be necessary to calculate tumor mutation burden (TMB).

The graphic below shows that payments for 1 or 2 genes could exceed the payment for 5-50 genes. It also illustrates that when we look at the code for 51+ genes, this code was almost always used for tests that actually have 300 or more genes.



What about Exome sequencing in tumors?

At this time, the AMA CPT doesn't have a Category I CPT code for exome sequencing, when this is used to evaluate solid tumors. While there is a code for clinical exome sequencing (81415), it includes a specific reference to germline testing, rather than tumor testing. Exome sequencing may become an area where new codes are needing, as publications on exome testing in tumors are picking up speed (Chakravarty and Solit 2021; Cobain et al. 2021; Hicks et al. 2021).

Coding for TMB?

There has never been a standalone code for TMB, and as of mid-2021, there is none in the AMA CPT pipeline, which takes about two years to produce a new CPT code. This likely means that TMB is being ordered, run, and billed as part of CGP, or under lab-specific PLA and ADLT codes and under code 81455 (51 genes or more). The other gene panel code, 81445, is for 50 genes or less, and this gene volume is too small to support statistically accurate TMB reporting (Chaudhary et al. 2018).

The TMB Horizon?

TMB is currently reported as mutations per exome, or increasingly commonly, mutations per megabase of DNA, with 1.5 or more Mb sequenced and a cutoff such 10 mutations per Mb (as used in 2020 by FDA). Areas of research are several. These include whether different cutpoints will be better selectors for different types of cancer (e.g. lung cancer vs melanoma), and whether direct mutation counts are the best metric or if there should be a calculation based on predicted protein antigenicity (e.g. adding machine learning or AI to TMB). For the near term, the oncology community seems to be settling on CGP sequencing with the add-on service of TMB reporting.

Approvals and Guidelines for Advanced Genomic Profiling

One of the most important developments in the last 3 years in oncology is the development of drugs (and genetic tests) that are tumor-agnostic (Lavacchi et al. 2020; Peng et al. 2021; Seligson et al. 2021). This means that the biomarker is a flag for use of an indicated drug in any of a wide range of solid tumors. The biomarker is not tumor-specific, nor is the drug it is associated with.

The FDA has approved cancer immunotherapies for both microsatellite-stability-high and TMB-high indications, most studies of both markers find more TMB-high cases than MSI-high cases. Because of the importance of TMB for more patients, the June 2020 approval of pembrolizumab (Keytruda) for TMB-high cancers (with ≥ 10 mutations/megabase of sequenced DNA), was a landmark event (Marcus et al. 2021). This approval was based on KEYNOTE-158, for TMB-high cancers (Marabelle et al. 2020). In this study, 102 (13%) of 790 patients had TMB-high status. On Keytruda monotherapy, objective response to therapy was almost **five times as high** in the TMB-high group (29% vs 6%). Even more important, the durability for responding patients was really meaningful. In half of these patients, the ongoing duration of response was ≥ 24 months, and that is truly a dramatic result for advanced cancer patients with no other options available. As of the March 2021 labeling, the FDA approval for Keytruda is for any adult or pediatric cancer of advanced stage, with high TMB, and where no other treatment options are available.

The KEYNOTE trial, as reported by Marabelle et al, is far from the only study of its type. Other authors have also published findings that support use of TMB, and immuno-oncology therapies, in diverse advanced cancers.

- Samstein et al. found that TMB was associated with longer overall survival in a population of 1662 patients with diverse histologies (Samstein et al. 2019).
- Valero et al. studied 10,233 patients with 17 cancer types, and also found that TMB was strongly associated with longer survival on IO therapy, but not with a standalone prognostic benefit (Valero et al. 2021).

Organizations Support Access to CGP

Numerous organizations support stronger access to CGP. In Fall 2020, the American Cancer Society and the patient association LUNGevity published a 46-page guide to **payer coverage policies for tumor biomarker testing**, conducted by the consulting group ADVI. While finding numerous gaps regarding panel coverage, especially outside of the Medicare program, these groups reported that immune-oncology therapies are difficult to manage with TMB-based diagnostics, as long as larger panels are not covered (American_Cancer_Society and LUNGevity ADVI 2020).

Organizational Efforts include LUNGevity, MYLUNG, and ACGP Coalition

- **LUNGevity.** In response, **LUNGevity** has launched a program to heighten awareness of the importance of genomic profiling to guide cancer treatment (Hopkins 2021a). This may be of particular importance in minority populations (Canexia_Genomeweb 2021; Ray 2021)2021, raising concerns about racial disparities and healthcare equity (National_Academy 2018).
- **MYLUNG.** Similarly, in 2021, McKesson, together with US Oncology, Southern Cancer Center, and other groups, launched the **MYLUNG** consortium (McKesson 2021). Concurrently, Amgen and molecular lab Neogenomics have partners in a program to expand access to biomarker testing in lung cancer (GenomewebStaff 2021). All of these initiatives aim to help overcome gaps in current diagnostic practices (Singh et al. 2020).

- ACCESS TO CGP. The ACGP Coalition is a coalition of the leading diagnostics companies and laboratory service providers that aims to collectively advocate for appropriate broad U.S. health insurance coverage of comprehensive genomic profiling (CGP) for patients living with advanced cancer. ACGP is designed to work in an inclusive and collaborative way to represent the views of a broad range of stakeholders, including patients, providers, academic centers and the pharmaceutical industry, that rely on diagnostic tests to inform the medical management of cancer patients including, where appropriate, the use targeted and immuno therapies. https://accesstocgp.com/

Across these independent efforts, we see echoes of what physician-journalist Elaine Schattner wrote in Forbes in 2018:

> *What's at issue is the right of all cancer patients—regardless of wealth—to obtain high-quality information about their conditions. Patients and their doctors rely on accurate results for choosing the right treatment.*
>
> *Without access to these tests, those whose cancers have mutations for which matched, precision oncology drugs are available are doomed to take old-style chemotherapy before they might even consider new options. (Schattner 2018)*

Major Guidelines Endorse CGP

Consistent with the FDA approval of TMB for immuno-oncology therapy in advanced cancer, TMB-H measurement is recommended in NCCN guidelines across a wide range of cancers, consistent with FDA labeling. These include the NCCN guideline for bone cancer (1.2021), breast cancer (1.2021), cervical cancer (1.2021), esophageal cancer (1.2021), gastric cancer (1.2021), head and neck cancers (1.2021), hepatobiliary cancer (4.2021), neuroendocrine cancers (1.2021), cancer of unknown primary (1.2021), ovarian cancer (3.2021), testicular cancer (1.2021), thyroid cancer (1.2021), uterine cancer (1.2021), and vulvar cancer (1.2021).

In March 2022, the American Society for Clinical Oncology (ASCO) released a guideline for CGP use across solid cancers; see (Chakravarty et al. 2022). Also in 2022, the Personalized Medicine Coalition released a position paper on clinical utility of genomic testing, with an emphasis on CGP testing in cancer patients (Pritchard et al. 2022).

4

Conclusions

Conclusions

This white paper has aimed to explain both **Comprehensive Genomic Profiling (CGP)** and **Tumor Mutation Burden (TMB).**

Comprehensive Genomic Profiling serves several purposes, including accurate assessment of all genes for which FDA-approved or NCCN-endorsed therapies are available, and identifying patients with rare genes where single-gene orders are impractical. This approach provides high-efficiency one-time genomic assessment when tissue is limited, and providing enough high-accuracy sequencing – typically over a megabase of DNA - to support a statistically accurate calculation of Tumor Mutation Burden.

TMB, in turn, is strongly associated both with higher rates of immediate drug response and better long-term outcomes on immuno-oncology drugs in patients with advanced cancers.

Although hundreds of genetic codes were created in the past decade, we saw that CGP and TMB coding and pricing is confusing and in some ways illogical. In 2022, we're still living with the odd logistics based on codes and prices that are little-changed since 2013. The coding system resulting in higher payments for either 2-4 gene tests or for large tests (>300) genes, and gave lower payments for 5-50 genes. The era of testing five or six single genes is lapsing, because immuno-oncology therapies are now well-established, and to serve these patients, TMB and CGP are well-established in FDA labeling and in cancer guidelines from the NCCN and ASCO. Oncologists need to select the best-suited patients for immuno-oncology therapies, and TMB requires a volume of sequencing that facilitates CGP analysis for several hundred genes. Diagnostic tests will be strongly contributory to this new generation of patient care, particularly if we can move away from an over-reliance on immunohistochemistry for PDL-1, which never performed very well as a biomarker for drug response (Grossman et al. 2021), even if it made a good biological target for drug development.

The consensus is converging on the idea that TMB testing most often outperforms PDL1 testing. And unlike PDL1 testing, TMB testing is likely to improve as superior methods evolve. In short, whether viewed from the perspective of (1) the wide clinical publications, (2) FDA approvals, (3) actions of cancer organizations, (4) the health disparities debate, or (5) clinical guidelines, we are rapidly arriving at a point where CGP is the appropriate genomic test for many patients with advanced cancers.

5

Bibliography

Bibliography

Adashek, J. J., et al. (2021). "Missing the target in cancer therapy." Nat Cancer 2: 369-371.

Allegretti, M., et al. (2018). "Tearing down the walls: FDA approves next generation sequencing (NGS) assays for actionable cancer genomic aberrations." J Exp Clin Cancer Res 37(1): 47.

AMA (2021). AMA CPT: Diagnostic Precision Medicine Coding and Payment. Meeting 7/2021; Report 12/201 (18pp).

American_Cancer_Society and LUNGevity

ADVI. (2020). "Payer coverage policies for tumor biomarker testing (46pp). (Accessed June 1, 2021).", from https://www.fightcancer.org/sites/default/files/ACS%20CAN%20and%20LUNGevity_Payer%20Coverage%20Policies%20of%20Tumor%20Biomarker%20Testing.pdf.

Ashford, M. (2016). "Foundation Medicine test has the potential to guide immunotherapy, ASCO studies suggest." Genomeweb June 9, 2016.

Baldo, B. A. and N. H. Pham (2020). "Non-targeted drugs for cancer therapy." Drug Allergy 9: 645-682.

Bazell, R. (1998). Her2: The Making of Herceptin., Random House.

Berger, M. F. and E. R. Mardis (2018). "The emerging clinical relevance of genomics in cancer medicine." Nat Rev Clin Oncol 15(6): 353-365.

Boyle, T. A., et al. (2021). "Guideline-Adherent Clinical Validation of a Comprehensive 170-Gene DNA/RNA Panel for Determination of Small Variants, Copy Number Variations, Splice Variants, and Fusions on a Next-Generation Sequencing Platform in the CLIA Setting." Front Genet 12: 503830.

Canexia_Genomeweb. (2021). "(WEBINAR) Disparities in precision oncology: Identifying barriers and moving toward a solution. (June 18, 2021). T. Ray, Moderator.", from Archive Link: https://brucedocumentblog.blogspot.com/2021/06/june-18-2021-precision-oncology-news.html.

Caris. (2021). "Profile Menu Brochure (CGP), June 1, 2021.", from https://www.carislifesciences.com/wp-content/uploads/2021/08/Profile-Menu-Brochure.pdf.

Chakravarty, D., et al. (2022). "Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion." J Clin Oncol: JCO2102767.

Chakravarty, D. and D. B. Solit (2021). "Clinical cancer genomic profiling." Nat Rev Genet 22(8): 483-501.

Chaudhary, R., et al. (2018). "A scalable solution for tumor mutational burden from formalin-fixed, paraffin-embedded samples using the Oncomine Tumor Mutation Load Assay." Transl Lung Cancer Res 7(6): 616-630.

Chawla, A., et al. (2018). "Estimated Cost of Anticancer Therapy Directed by Comprehensive Genomic Profiling in a Single-Center Study." JCO Precis Oncol 2.

CMS. (2021). "National Coverage Determination (NCD) 90.2, Next Generation Sequencing. (February 2018; updated January 2020).", from https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=372.

Cobain, E. F., et al. (2021). "Assessment of Clinical Benefit of Integrative Genomic Profiling in Advanced Solid Tumors." JAMA Oncol 7(4): 525-533.

Conroy, J. M., et al. (2021). "A scalable high-throughput targeted next-generation sequencing assay for comprehensive genomic profiling of solid tumors." PLoS One 16(12): e0260089.

Cristescu, R., et al. (2022). "Tumor mutational burden predicts the efficacy of pembrolizumab monotherapy: a pan-tumor retrospective analysis of participants with advanced solid tumors." J Immunother Cancer 10(1).

Dong, A., et al. (2021). "PD-L1 versus tumor mutation burden: Which is the better immunotherapy biomarker in advanced non-small cell lung cancer?" J Gene Med 23(2): e3294.

Doroshow, D. B., et al. (2021). "PD-L1 as a biomarker of response to immune-checkpoint inhibitors." Nat Rev Clin Oncol 18(6): 345-362.

Dracopoli, N. C. and M. S. Boguski (2017). "The Evolution of Oncology Companion Diagnostics from Signal Transduction to Immuno-Oncology." Trends Pharmacol Sci 38(1): 41-54.

Du, F. and Y. Liu (2022). "Predictive molecular markers for the treatment with immune checkpoint inhibitors in colorectal cancer." J Clin Lab Anal 36(1): e24141.

Endris, V., et al. (2019). "Measurement of tumor mutational burden (TMB) in routine molecular diagnostics: in silico and real-life analysis of three larger gene panels." Int J Cancer 144(9): 2303-2312.

Fabrizio, D. A., et al. (2018). "Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition." J Gastrointest Oncol 9(4): 610-617.

Fancello, L., et al. (2019). "Tumor mutational burden quantification from targeted gene panels: major advancements and challenges." J Immunother Cancer 7(1): 183.

FDA. (2013a). "Qiagen Therascreen EGFR Test. (P120022) (July 12, 2013)." from https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start_search=1&PMANumber=P120022&SupplementType=NONE.

FDA. (2013b). "Roche Cobas EGFR Mutation Test (P12019) (May 14, 2013).", from https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P120019.

FDA. (2017). "MSK IMPACT Test (510k) (June 1, 2021).", from https://www.accessdata.fda.gov/cdrh_docs/reviews/den170058.pdf.

FDA. (2020a). "FDA approves pembrolizumab for adults and children with TMB-H solid tumors. (June 16, 2020; press release).", from https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors.

FDA. (2020b). "Foundation One, PMA P170019S017B. (October 23, 2020).", from https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019S017B.pdf.

FDA. (2020c). "PGDx elio(tm) test. K192063.", from https://www.accessdata.fda.gov/cdrh_docs/reviews/K192063.pdf.

FDA. (2021a). "Keytruda (pembrolizumab) labeling. 105pp. Update 05/2021.", from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s097lbl.pdf#page=101.

FDA. (2021b). "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (Visited June 1, 2021).", from https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

Gautam, S., et al. (2021). "Clinical and utilization outcomes associated with tumor mutational burden in a real-world pan-tumor population." J Comp Eff Res.

GenomewebStaff (2021). "Amgen, NeoGenomics Partner to Expand Biomarker Testing Access in NSCLC." Genomeweb April 19, 2021.

Greenman, C., et al. (2007). "Patterns of somatic mutation in human cancer genomes." Nature 446(7132): 153-158.

Grossman, J. E., et al. (2021). "Is PD-L1 a consistent biomarker for anti-PD-1 therapy? The model of balstilimab in a virally-driven tumor." Oncogene 40(8): 1393-1395.

Guo, W., et al. (2020). "An Exon Signature to Estimate the Tumor Mutational Burden of Right-sided Colon Cancer Patients." J Cancer 11(4): 883-892.

Hanamura, N. and A. Aruga (2014). "Global development strategy for companion diagnostics based on the usage and approval history for biomarkers in Japan, the USA and the EU." Per Med 11(1): 27-40.

Harvey, M. J., et al. (2021). "Budget Impact Analysis of Comprehensive Genomic Profiling in Patients With Advanced Non-Small-Cell Lung Cancer." JCO Precis Oncol 5: 1611-1624.

Hicks, J. K., et al. (2021). "Integrating Somatic and Germline Next-Generation Sequencing Into Routine Clinical Oncology Practice." JCO Precis Oncol 5.

Hopkins, C. (2021a). "LUNGevity Aims for Widespread Comprehensive Biomarker Test Access With New Patient-Facing Campaign." Genomeweb May_14_2021.

Hopkins, C. (2021b). "Oncologists, patients still face unpredictable payor coverage for braod tissue NGS panels." Genomeweb (May 17, 2021).

Hsiao, S. J., et al. (2018). "The History and Impact of Molecular Coding Changes on Coverage and Reimbursement of Molecular Diagnostic Tests: Transition from Stacking Codes to the Current Molecular Code Set Including Genomic Sequencing Procedures." J Mol Diagn 20(2): 177-183.

Hsiao, S. J., et al. (2020). "Clinical Utilization, Utility, and Reimbursement for Expanded Genomic Panel Testing in Adult Oncology." JCO Precis Oncol 4: 1038-1048.

Illumina. (2021). "Comprehensive Genomic Profiling (Website). (Accessed June 1, 2021)." from https://www.illumina.com/areas-of-interest/cancer/clinical-cancer-research/cgp.html.

Jacob, J., et al. (2021). "Comprehensive genomic profiling of histologic subtypes of urethral carcinomas." Urol Oncol 39(10): 731 e731-731 e715.

Johnston, K. M., et al. (2020). "Comprehensive genomic profiling for non-small-cell lung cancer: health and budget impact." Curr Oncol 27(6): e569-e577.

Jorgensen, J. T. (2013). "Companion diagnostics in oncology - current status and future aspects." Oncology 85(1): 59-68.

Jorgensen, J. T. and M. Hersom (2018). "Clinical and Regulatory Aspects of Companion Diagnostic Development in Oncology." Clin Pharmacol Ther 103(6): 999-1008.

Kim, H., et al. (2021). "Clinical sequencing to assess tumor mutational burden as a useful biomarker to immunotherapy in various solid tumors." Ther Adv Med Oncol 13: 1758835921992992.

Labrie, M., et al. (2022). "Therapy resistance: opportunities created by adaptive responses to targeted therapies in cancer. (Epub)." Nature Rev Cancer.

Lavacchi, D., et al. (2020). "Tumor-Agnostic Treatment for Cancer: When How is Better than Where." Clin Drug Investig 40(6): 519-527.

Lennerz, J. K., et al. (2016). "Health Care Infrastructure for Financially Sustainable Clinical Genomics." J Mol Diagn 18(5): 697-706.

Li, Y., et al. (2020). "Translating Immuno-oncology Biomarkers to Diagnostic Tests: A Regulatory Perspective." Methods Mol Biol 2055: 701-716.

Looney, A. M., et al. (2020). "Tumour-agnostic therapies." Nat Rev Drug Discov 19(6): 383-384.

Lu, S., et al. (2021). "Comprehensive genomic profiling and prognostic analysis of cervical gastric-type mucinous adenocarcinoma." Virchows Arch 479(5): 893-903.

LUNGevity. (2020). "Pan-Cancer Consortium Moves to Clarify and Promote Consistent Use of Common Terms for Biomarker and Germline Genetic Testing." from https://www.lungevity.org/news/media-releases/pan-cancer-consortium-moves-to-clarify-and-promote-consistent-use-of-common.

Marabelle, A., et al. (2020). "Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study." Lancet Oncol 21(10): 1353-1365.

Marcus, L., et al. (2021). "FDA Approval Summary: Pembrolizumab for the treatment of tumor mutational burden-high solid tumors." Clin Cancer Res Epub.

McGrail, D. J., et al. (2021). "High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types." Ann Oncol 32(5): 661-672.

McKesson. (2021). "MYLUNG Study Launches, Aiming to Advance Use of Precision Medicine for Metastatic Non-Small Cell Lung Cancer Patients (Feb. 4, 2021)." from https://www.mckesson.com/About-McKesson/Newsroom/Press-Releases/2021/MYLUNG-Study-Launches-Advance-Precision-Medicine-Lung-Cancer-Patients/.

Meng, G., et al. (2022). "Predictive value of tumor mutational burden for immunotherapy in non-small cell lung cancer: A systematic review and meta-analysis." PLoS One 17(2): e0263629.

Merino, D. M., et al. (2020). "Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project." J Immunother Cancer 8(1).

National_Academy (2018). Understanding Disparities in Access to Genomic Medicine: Proceedings of a Workshop.

O'Meara, T. A. and S. M. Tolaney (2021). "Tumor mutational burden as a predictor of immunotherapy response in breast cancer." Oncotarget 12(5): 394-400.

OmniSeq. (2021). "OmniSeq INSIGHT Test (June 1, 2021).", from https://www.omniseq.com/omniseq-insight/.

Palmeri, M., et al. (2022). "Real-world application of tumor mutational burden-high (TMB-high) and microsatellite instability (MSI) confirms their utility as immunotherapy biomarkers." ESMO Open 7(1): 100336.

Patel, Y. P., et al. (2021). "Health and Budget Impact of Liquid-Biopsy-Based Comprehensive Genomic Profile (CGP) Testing in Tissue-Limited Advanced Non-Small Cell Lung Cancer (aNSCLC) Patients." Curr Oncol 28(6): 5278-5294.

Peng, Y., et al. (2021). "Review and Prospect of Tissue-agnostic Targeted Strategies in Anticancer Therapies." Curr Top Med Chem 21(5): 404-425.

Pennell, N. A. (2019). "Economic Impact of Next-Generation Sequencing Versus Single-Gene Testing to Detect Genomic Alterations in Metastatic Non–Small-Cell Lung Cancer Using a Decision Analytic Model." JCO Precis Oncol Epub.

Pinato, D. J., et al. (2020). "Applicability of Routine Targeted Next-generation Sequencing to Estimate Tumor Mutational Burden (TMB) in Patients Treated With Immune Checkpoint Inhibitor Therapy." J Immunother 43(2): 53-56.

Pritchard, D., et al. (2022). "Clinical Utility of Genomic Testing in Cancer Care." JCO Precis Oncol 6: e2100349.

Quinn, B. (2018). "J Molec Dx: A Quartet of Important Articles on Genomics Reimbursement." Discoveries in Health Policy June 29, 2018.

Ray, T. (2021). "ASCO Studies Highlight Systemic, Racial Inequities in Lung Cancer Biomarker Testing." Genomeweb (June 8, 2021).

Rousseau, B., et al. (2021). "The Spectrum of Benefit from Checkpoint Blockade in Hypermutated Tumors." N Engl J Med 384(12): 1168-1170.

Samstein, R. M., et al. (2019). "Tumor mutational load predicts survival after immunotherapy across multiple cancer types." Nat Genet 51(2): 202-206.

Schattner, E. (2018). "All cancer patients should have access to genomic testing." Forbes March 6, 2018.

Scheuner, M. T., et al. (2021). "Laboratory business models and practices: implications for availability and access to germline genetic testing." Genet Med.

Schrock, A. B., et al. (2019). "Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer." Ann Oncol 30(7): 1096-1103.

Seligson, N. D., et al. (2021). "Developing Drugs for Tissue-Agnostic Indications: A Paradigm Shift in Leveraging Cancer Biology for Precision Medicine." Clin Pharmacol Ther 109(2): 334-342.

Singh, A. P., et al. (2020). "Impact and Diagnostic Gaps of Comprehensive Genomic Profiling in Real-World Clinical Practice." Cancers (Basel) 12(5).

Stenzinger, A., et al. (2019). "Tumor mutational burden standardization initiatives: Recommendations for consistent tumor mutational burden assessment in clinical samples to guide immunotherapy treatment decisions." Genes Chromosomes Cancer 58(8): 578-588.

Stratton, M. R., et al. (2009). "The cancer genome." Nature 458(7239): 719-724.

Sung, W. W. Y., et al. (2021). "Tumor mutational burden as a tissue-agnostic biomarker for cancer immunotherapy." Expert Rev Clin Pharmacol 14(2): 141-143.

Trosman, J. R., et al. (2020). "Insights From a Temporal Assessment of Increases in US Private Payer Coverage of Tumor Sequencing From 2015 to 2019." Value Health 23(5): 551-558.

Trosman, J. R., et al. (2018). "From the Past to the Present: Insurer Coverage Frameworks for Next-Generation Tumor Sequencing." Value Health 21(9): 1062-1068.

Twomey, J. D. and B. Zhang (2021). "Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics." AAPS J 23(2): 39.

Valero, C., et al. (2021). "The association between tumor mutational burden and prognosis is dependent on treatment context." Nat Genet 53(1): 11-15.

Vanderwalde, A., et al. (2018). "Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients." Cancer Med 7(3): 746-756.

Varesio, C., et al. (2021). "Diagnostic Yield and Cost-Effectiveness of "Dynamic" Exome Analysis in Epilepsy with Neurodevelopmental Disorders: A Tertiary-Center Experience in Northern Italy." Diagnostics (Basel) 11(6).

Verma, M. (2014). "Molecular profiling and companion diagnostics: where is personalized medicine in cancer heading?" Per Med 11(8): 761-771.

Wagener-Ryczek, S. and R. Buettner (2021). "The value of tumor mutational burden to select patients for immunotherapy." Expert Rev Anticancer Ther 21(1): 1-3.

Wang, C., et al. (2022). "Biomarkers for predicting the efficacy of immune checkpoint inhibitors." J Cancer 13(2): 481-495.

Wikipedia. (2021). "Trastazumab. (Visited June 1, 2021).", from https://en.wikipedia.org/wiki/Trastuzumab.

Yachida, S., et al. (2022). "Comprehensive Genomic Profiling of Neuroendocrine Carcinomas of the Gastrointestinal System." Cancer Discov 12(3): 692-711.

BRUCE QUINN ASSOCIATES LLC

HEALTH INNOVATION MADE REAL.

Innovators in healthcare have a triple aim: innovation, high impact on healthcare, and return on investment.

Payers and providers have a triple aim: improving quality, improving access, reducing cost.

Too often, there's a collision between healthcare innovation and the legacy healthcare systems. Clash rather than synergy.

As experts in health innovation strategy, we spend our time understanding that complex legacy system. We can bring that expertise to your company to solve business roadblocks.

Federal health policy explained. Changes in hospital, physician, and other payment systems unwound and deciphered. Add the wisdom to deliver the right advice the right way, and the scientific insight to understand your product.

Bruce Quinn, MD, PhD is an expert on health reform, innovation, and Medicare policy. He helps both large and small companies understand and overcome hurdles to commercialization, as well as craft business strategies for a changing environment.

1

Understanding Comprehensive Genomic Profiling (CGP)

Understanding Comprehensive Genomic Profiling (CGP)

1