Programmatic Efforts Increase Adoption of Genomic Precision Medicine in Cancer Care in a Community Cancer Center

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PURPOSE The adoption of precision medicine (PMed) depends on the critical curation of data and interpretation of genomic results. Herein, we sought to study the effect of a coordinated multidisciplinary program to assess results in a community cancer center clinic.

METHODS In a retrospective review from July 2018 to July 2021, we analyzed the implementation of a multidisciplinary PMed program in a tertiary referral community cancer center. Germline genetics test results have been reviewed since 2017.

RESULTS A total of 3,131 tumor samples were analyzed by large panel somatic genomic testing through commercial laboratories during the study period. The number of reviewed cases rose from 661 in the first year to 1,532 in year 3. Additional recommendations beyond what was reported by the commercial laboratory were made in 42.9% of cases. Referrals to the hereditary cancer program for germline testing increased by 32% from the 2017 baseline. Process improvement efforts reduced the rate of DNA quantity nonsufficient for testing to 3.3% compared with a national average of 4.89%. The average time from receipt of orders to issuing of a report of the somatic panel was 15.5 days, compared with 19.1 days for other institutions using the same laboratory. The PMed team has been critical in support of clinical research by assisting in trial procurement and feasibility assessment to the identification of patients for clinical trials.

CONCLUSION The use of somatic genomic testing is increasing at our cancer center. Education and in-depth analysis of the data are valued by cancer physicians. The development and implementation of a PMed program has demonstrated improved physicians' understanding of molecular testing, resulting in improved outcomes for patients.

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INTRODUCTION

In oncology, precision medicine (PMed) promises to foster the delivery of more effective medications targeting tumor mutations to improve outcomes for patients with less toxicity. Recent advances in genomic testing technologies, allowing for rapid results at a reduced cost, make clinical applications tractable. Commercial or in-house laboratories provide next-generation sequencing (NGS) tests to identify actionable variants to guide targeted therapy.[1] Molecularly targeted drug treatments have become standard of care for several cancers, and NGS may identify relevant somatic variants affecting treatment in 40%-94% of patients with advanced cancer.[2]

Despite an increasing repertoire of available targeted drugs, several studies have shown that a relatively low proportion of patients' treatments are directed by NGS testing.[2] The interpretation of the genomic data requires a sophisticated knowledge of genomics, and the optimal management of oncology patients is enhanced by the availability of precise treatments.[3] A barrier to adoption includes a lack of complete understanding among providers regarding the usefulness and methods of application of NGS testing. Clinicians are aware that they require additional education. Medical oncologists, when surveyed, identified a need for clinical decision support in the interpretation and application of genomics as their greatest need to facilitate the adoption of PMed.[4]

Previous investigators have suggested a biomarker-driven decision support system including molecular tumor boards (MTBs) and a technological scientific platform to automate the curation and interpretation of NGS data.[5] Oncology MTBs frequently improve outcomes by offering therapeutic and clinical trial recommendations, leading to an overall response rate of up to 67%.[1] To assist in adopting NGS testing at our

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CONTEXT

Key Objective

The use of somatic genomic profiling is increasing as the technology advances and the cost decreases. Although precision medicine (PMed) offers the potential for improved outcomes for patients with advanced cancer, barriers exist. The purpose of this study is to evaluate the impact of a PMed program supporting clinicians with the interpretation of genomic data and educational outreach.

Knowledge Generated

A coordinated PMed program supporting the cancer center physicians may overcome some of the barriers to adopting genomic testing. The team includes a physician leader, molecular pathologist, clinical genomic scientist, licensed genetic counselors, and medical geneticist.

Relevance

The PMed team's effort in coordinating the testing, providing education, and interpreting the genomic and genetic data is valued by physicians. The adoption of PMed is enhanced due to better physicians' understanding of the clinical utility of molecular testing.

cancer center, a coordinated PMed program was established. The team provided education, clinical decision support, and operations management with process improvement to facilitate the use of somatic and germline NGS clinical tests. We, herein, describe some successes and challenges and show that a robust multidisciplinary PMed program has supported and accelerated the adoption of PMed in a community cancer center.

METHODS

A multidisciplinary PMed team was established to support oncology care on behalf of providers. The PMed team members included a physician leader with an extensive clinical and laboratory background in genomics, a clinical genomics scientist who has a PhD in human genetics, three licensed genetic counselors who are highly trained in the field of oncology, and a pathologist who is fellowship-trained in molecular pathology. The team also included a medical geneticist who leads the high-risk early detection programs at our hospital.

Genomic large panel testing was done primarily through a single commercial vendor selected after reviewing offerings from commercial laboratories accredited by the College of American Pathologists and Clinical Laboratory Improvement Amendments. Tumor testing was NGS of the entire exons of over 600 cancer-relevant genes with the issue of a curated report. Later iteration of the test included whole-exome and transcriptome sequencing to better detect fusions. Reflex testing criteria were established by multidisciplinary teams of oncologists (Table 1). For example, to develop reflex criteria for lung cancer, medical oncologists, pulmonologists, radiation oncologists, and thoracic surgeons reviewed the literature and agreed on criteria for NGS testing. The reflex criteria were integrated into the pathology workflow. The clinical pathologist ordered NGS testing and submitted samples as part of a standard workflow if patients met the criteria. For patients whose tumors did not meet reflex testing criteria, physicians could request NGS testing if indicated on the basis of their own clinical evaluation. Although the majority of tests were performed by a single commercial laboratory, physicians could request their laboratory of choice.

In-house, in-depth analyses and curation of the commercial laboratories' reports were uniformly done by our clinical genomics scientist, in collaboration with the physician leader and the molecular pathologist. In some cases, the

TABLE 1. NGS Pathology Reflex Testing Protocol for Solid Tumors

Tumor Type	Comment
Metastatic GI adenocarcinoma	Metastatic
Cholangiocarcinoma, bile ducts, and gallbladder	All stages
Pancreatic adenocarcinoma	All stages
Breast carcinoma	Stage IV or recurrent breast cancers
Urothelial carcinoma	Stage IV cancers and all muscle-invasive bladder cancers
Prostate adenocarcinoma	Stage IV
Non–small-cell lung carcinoma	Stages IB or higher
Sarcoma	All sarcomas of intermediate to high grade[a]
Brain gliomas/GBM	Low-grade gliomas and GBMs
Melanoma	Stage III and IV melanomas
Gynecologic cancers	All recurrent cancers, all stage IV cancers
Thyroid cancer	Anaplastic, poorly differentiated or medullary carcinomas
Head and neck cancers	Stage III and IV cancers, all P16 negative

Abbreviation: GBM, glioblastoma.

[a]Resection specimens only; if tumors were unresectable, then a core needle specimen was submitted.

Binary Alignment Map files from the sequencing laboratory were required. Variant classification as pathogenic or likely pathogenic was confirmed or, in some cases, changed on the basis of review of literature and publicly available genomic databases. Assessment of variants for actionability included US Food and Drug Administration (FDA)–approved biomarker-drug associations, annotation to off-label use of FDA-approved drugs, clinical trials, or even with drugs available for compassionate use.

Referral to genetic counselors for germline genetic testing was recommended if a founder mutation was present on somatic tumor testing, suggesting a possible germline event. Notable findings were communicated to treating oncologists by phone or by secure text messaging. Genetic counselors saw the patients and ordered germline genetic testing on the basis of personal and family history. In addition, we initiated a clinical research protocol for patients who did not meet insurer criteria for genetic counseling and testing but were suspected of harboring germline mutations on the basis of their somatic sequencing.

When we started our PMed program, a series of 4-hour evening seminars were offered to medical staff, and Continuing Medical Education credits were provided. Seminar topics included an introduction to PMed, the basics of genetics and genomics, hereditary cancer syndromes, the molecular pathology of cancer, sequencing technologies, and a discussion of genetic and genomic variant interpretation. A monthly MTB was established, during which two or three recent patients were discussed in detail to highlight notable genomic events and recent developments in targeted drug therapy.

Additionally, a discussion of the results from large gene panel testing and the importance of the findings toward the selection of treatment were discussed at over 30 subspecialty tumor boards (TBs) each month. The genomics of each patient's tumor was presented including an overview of the background molecular biology of each actionable biomarker and clinical trial options. We offer consultations to physicians to review patients' genomic results. Physicians and staff attending TBs completed a survey using a 1-7 Likert scale.[6]

The PMed staff facilitated the coordination of testing and, at times, helped with the procurement of additional tissue samples (when the initial sample did not meet quantity or quality requirements for successful sequencing), orthogonal testing to confirm equivocal or unusual results or the reconciliation of multiple attempts discrepant NGS panel tests. NGS could assist in the assignment of tumor histologic type or primary site for the tumors of uncertain origin. When TB discussions led to a conclusion that sequencing might be beneficial for a patient, the PMed staff assisted in follow-up to assure that an appropriate sample was identified and submitted. A prospective PMed dashboard of programmatic activity started during the third quarter of 2018 tracked the number of additional recommendations beyond those that were made within the report, the cases presented at TBs, recommendations for genetic counseling, cases reviewed, and the tests coordinated by the PMed team.

RESULTS

The accumulated dashboard data from tumor samples analyzed by large panel somatic genomic testing through commercial laboratories showed a rapid increase in the number of tests reviewed over the course of our study (Fig 1).

Implementation of reflex testing on the basis of pathology and clinical stage was likely a major driver of the increase in

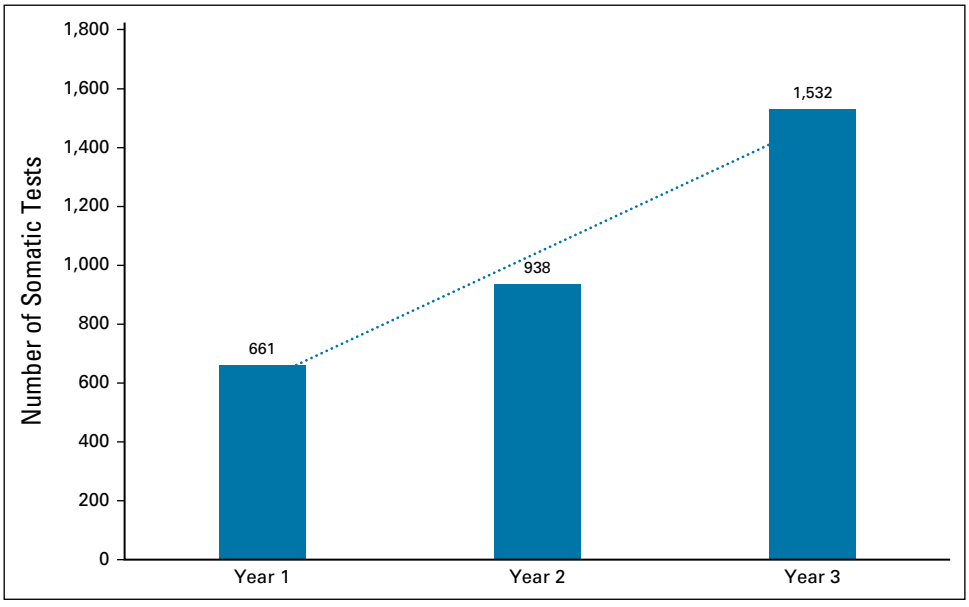

FIG 1. The number of somatic large genomic panel sequencing tests increased markedly during our study: 661 in year 1 (July 1, 2018, to June 30, 2019), 938 in year 2 (July 1, 2019, to June 30, 2020), and 1,532 in year 3 (July 1, 2020, to June 30, 2021).

testing. The most common cancers sequenced were non–small-cell lung cancer (21.5%), gynecological cancers (18.4%), head and neck cancers (7.9%), and brain tumors (7.7%; Fig 2).

Our in-house, in-depth curation made additional recommendations beyond those within the commercial laboratory reports in 42.9% of cases. These recommendations included potential treatment options with drugs that are FDA-approved for another indication or additional appropriate clinical trial options not identified by the commercial report on the basis of compelling biological or clinical evidence. Additionally, referral to genetic counseling for germline testing on the basis of the somatic pathogenic mutations was recommended for 11.2% of patients whose tumor harbored a mutation that could be germline. In some cases, modifications to the clinical pathology diagnosis were made because of somatic molecular profiling results. For example, a patient with a spinal lesion was presented with a TB. Subsequent testing identified *BRAF* V600E mutation allowing for a diagnosis of Erdheim-Chester disease to be established. For another patient presented with a primary of unknown origin, a diagnosis of melanoma was established on the basis of the identification of *RAC1* and *NRAS* mutations and subsequent confirmatory immunohistochemistry.

In-house, in-depth curation was essential to our efforts because we observed that many oncologists did not have sufficient knowledge or time to devote toward in-depth analysis of molecular testing results. For example, a discussion at a TB involved a patient whose lung cancer harbored a c*MET* amplification. Although a drug-gene association exists between c*MET* and the drug capmatinib, it is, however, approved only for exon 14 skipping mutations and therefore would not have been appropriate for this patient. An alternative treatment with crizotinib was recommended.[7] In another example, a somatic *HOXB13* gene mutation in a female patient with colorectal cancer was identified. Germline testing confirmed this mutation. Mutations in *HOXB13* are associated with an increased risk of prostate cancer, so although this patient did not directly benefit from this finding, she had two close male relatives who did benefit from the germline testing for this variant.

The total number of germline genetic tests conducted increased by 71% from 2014 to 2020 and by 32% from the 2017 baseline in our study (Fig 3). Interestingly, 24% of patients who were recommended for and subsequently tested harbored germline pathogenic mutations in 2020. A surrogate marker of the adoption of genetic counseling and genetic testing was the increase in testing for indications

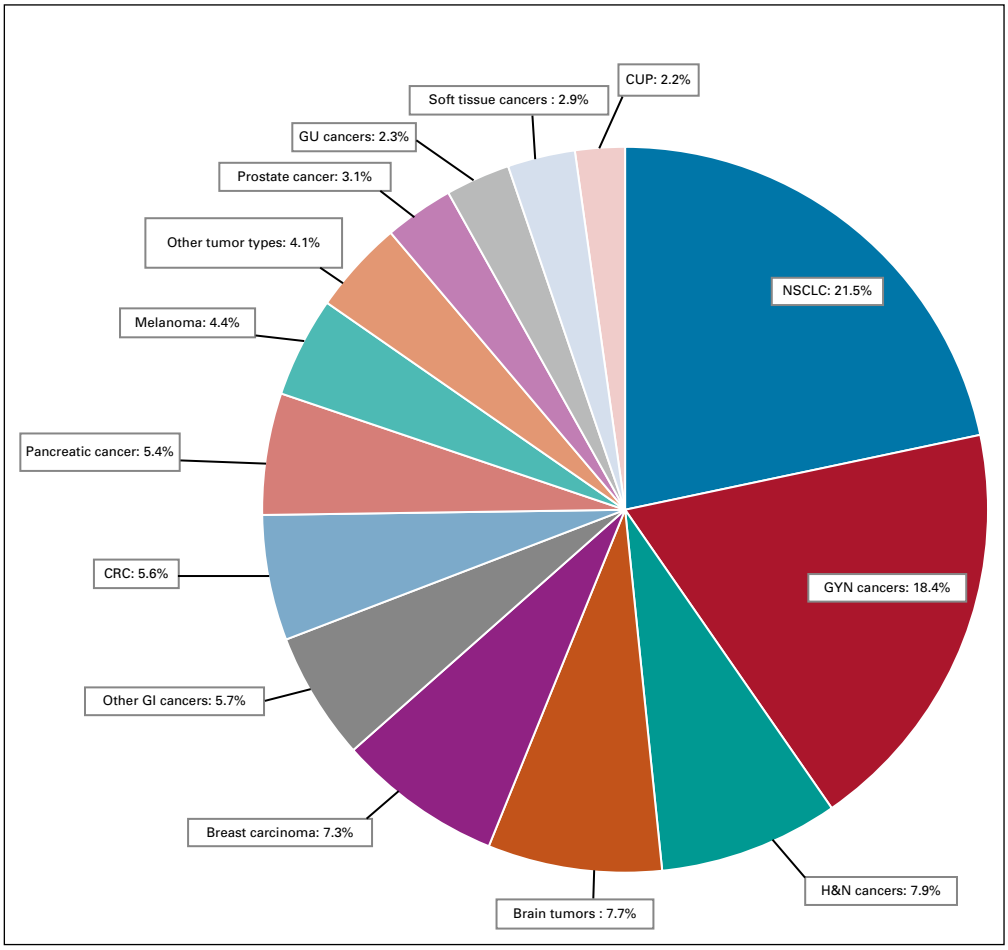

FIG 2. Hoag cancer cases by tumor type. CRC: colorectal cancer; CUP: cancer of unknown primary; GU cancers, genitourinary cancers; Gyn cancers: gynecologic cancers; H&N cancers, head and neck cancers; NSCLC, non–small-cell lung cancer.

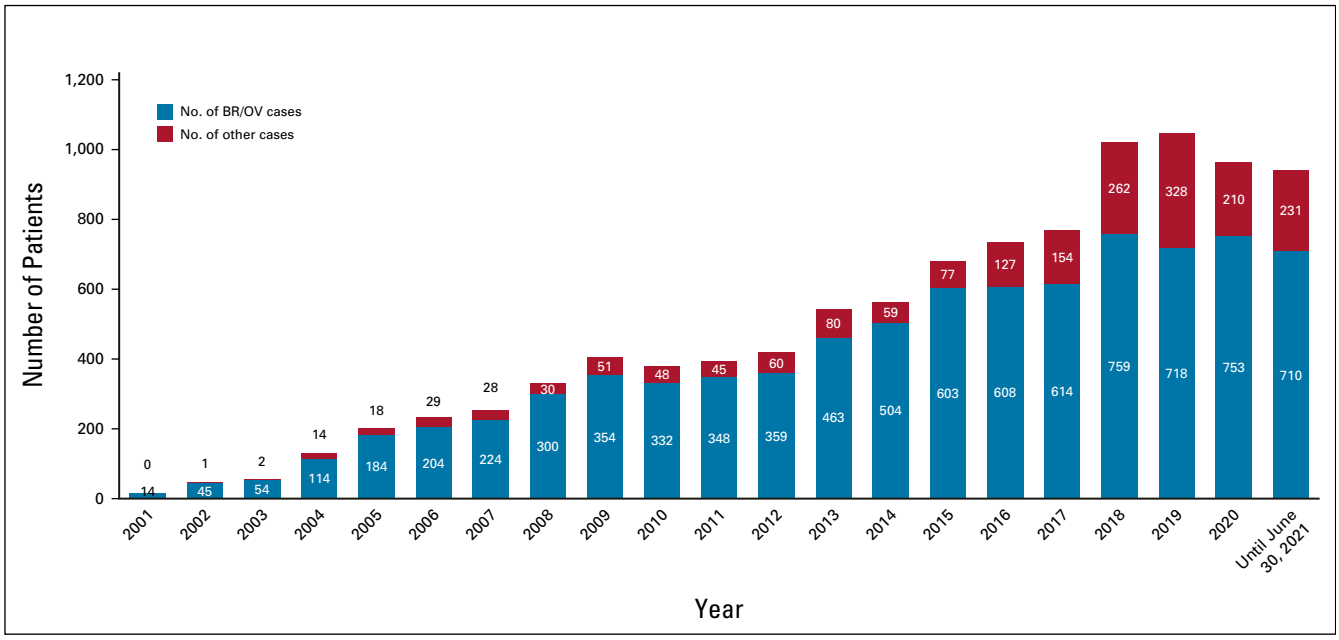

FIG 3. Genetic testing referrals since 2001. The number of patients referred for genetic counseling and testing has increased over the past 20 years. The proportion of patients referred for indications other than BR and OV cancer cases has also increased in recent years. BR cancer, breast cancer; OV cancer, ovarian cancer.

other than either breast cancer or ovarian cancer. Testing for these indications has been driven in large part due to advocacy and education efforts nationally. We observed that the proportion of patients referred with cancers other than breast or ovarian cancer rose by 66% since 2017 (Fig 3).

At the beginning of our PMed program, we had a total of 57 attendees, including 43 physicians, at an educational seminar series. Ongoing educational efforts included discussions of the molecular findings of 672 cases of subspecialty cancer TBs and the MTBs. The team has received 563 consultation requests in 3 years. Requests for assistance in the interpretation of molecular testing have increased 107.5% from the third quarter of 2018 to the third quarter of 2021. This metric is viewed as a barometer of acceptance of PMed services by oncologists and a tacit indication of clinic utility. An internal survey directly assessed the opinion of 41 physicians from seven cancer-related specialties who rated the PMed program's usefulness as 6.6 on a 1 to 7 Likert scale.

The PMed team coordinated the requisition and submission of 448 somatic sequencing tests. Since the PMed program was started, the rate of samples submitted with DNA quantity insufficient for testing was 3.3% compared with 4.9% across the laboratories. The average time from receipt of orders for testing until a report is issued with somatic molecular panel results was 15.5 days, compared with 19.1 days for all other institutions using the same commercial laboratory. Improving and expediting the process of preparing the samples and sending them to the laboratory helped our program reduce the time to activate the sample at the somatic laboratory and thus the overall turnaround time of testing. The vendor laboratory turnaround time is not under the PMed program's control, although the preparation time is. This can be interpreted as a success because of operational and process improvements by our pathology team.

DISCUSSION

The application of genomic information into clinical practice has evolved over the past two decades. The increased use of an NGS-based testing has helped oncologists to get closer to fulfilling the promise of PMed, namely more effective and less toxic targeted therapy. The availability of annotated results of the sequencing of panels of several hundred cancer-relevant genes in a rapid time frame and at a relatively low cost has driven increased adoption in clinical practice. Matching the oncologic treatments to the genomic data has improved outcomes in both solid tumors and hematological malignancies,[8] yet hurdles remain toward implementing PMed in community practices. Adoption of NGS testing in the community is critical because most patients with cancer in the United States are treated in community practices rather than in academic medical centers.[9] Our cancer center leadership determined that increased adoption of PMed was a goal and this decision led to the formation of our program.

Oncologists recognize the complexity of genomic information and the decisions around the application of knowledge in the selection of drug treatment. We propose a solution that has been effective in our community cancer

center. We have a multidisciplinary team of experts to assist with the selection of appropriate testing and the interpretation of the resulting genomic data. Our center did not mandate a particular genomic testing laboratory but did select a preferred vendor relationship for reflex and ad hoc testing. This partnership facilitated data exchange and operational improvements. Being a relatively high-volume customer with the testing laboratory gave our PMed team the ability to better interact with the laboratory scientists and provide feedback on laboratory reporting. There have been opportunities for joint publications with the testing laboratory on the basis of data sharing and participation in clinical trials with novel targeted agents.

Data establishing the clinical utility, improved outcomes, and cost benefit of molecular tumor profiling will ultimately drive the adoption of NGS testing broadly. Preliminary data from a review of real-world data from an MTB at a single site showed that expert recommendations when adopted were associated with longer progression-free survival and overall survival.[10] A prospective clinical trial (MOSCATO 01) indicated that high throughput genomic analysis could lead to a better outcome in patients with advanced cancer; they found that median overall survival in patients treated with targeted therapies was 11.9 months with an objective response of 11%.[11] In our center, an additional indicator of clinical utility was the increased orders for somatic genomic testing by physicians. Application of NGS-testing, however, requires at least a working knowledge of the testing modalities available, the limitations of particular tests, and the interpretation of results returned. In all, our PMed team was able to analyze 3,131 tumors and report additional recommendations because of a more in-depth analysis of the data in 42.9% of tumors. The adoption of molecular testing was enhanced by direct observation of important findings for patients. One example is a patient with recurrent unresectable thyroid cancer who, after seeing several physicians, was referred for evaluation at our center. She underwent molecular profiling, and her tumor exhibited an *NTRK* fusion. She was started on larotrectinib with salutary effect.

Reflex protocols drove increased testing. Criteria on the basis of pathology and clinical stage were agreed to by subspecialty oncologists. Efforts at education within our cancer center also facilitated adoption by making the complex jargon, concepts, and annotation more understandable. Individual consultative services were used with increasing frequency over the study period, suggesting that physicians saw value in the services for themselves and their patients. Our data show that the implementation of the oncology PMed program was viewed as a success by surveyed physicians in our cancer center.

Previous publications have shown that approximately 5%-10% of patients with advanced cancers harbor a cancer-related germline variant.[12] While some laboratories, such as MSK-IMPACT, use somatic-germline subtraction and have access to germline data, other laboratories do not, including Foundation Medicine and Caris Life sciences. Consequently, inferring possible germline variants from somatic-only NGS might assist in identifying patients who should undergo genetic counseling and testing. The American College of Medical Genetics guidelines offer recommendations for testing on the basis of clinical criteria, but adherence by practitioners to these guidelines is variable.[13] The referral of patients with suspected germline variants on the basis of somatic NGS could then be additive to existing guidelines if used routinely. Our protocol is to alert the treating physician when we observe a somatic mutation that might be a germline variant.

There are limitations to our study. There is no control group of a similar hospital community cancer center where a PMed program was not established, so it is unknown whether the adoption of NGS-testing would have been as robust as reported here without similar efforts. In our case, the adoption of NGS testing increased when oncologists understood and saw how the application of genomics benefitted patients they were treating. This was largely experiential and anecdotal. As was the case for laparoscopic gallbladder surgery where adoption did not depend on the findings of a prospective randomized trial; instead, the results were evident to doctors and patients. Not all payors are adopting NGS testing equally, primarily because of a lack of sufficient data on the value of such testing on the basis of the clinical benefit and the cost of subsequent genomically informed treatments. Two local Accountable Care Organizations declined to participate in reflex testing for their patients and would not preauthorize testing for any group of patients. Instead, these Accountable Care Organizations established contracts with laboratories that were different from our preferred laboratory and required oncologists to see their covered patients before seeking preauthorization for NGS testing on an individual basis. Our results are preliminary, and there remain opportunities for improvements. Outcome and financial impact data are needed to demonstrate that PMed is providing value in health care. To this end, improved informatics capabilities are needed. The field has focused on DNA-sequencing, but we predict increased use of proteomics, RNA-sequencing, and a multiomic approach toward treatment decisions. We also did not track circulating tumor DNA assays, as these newer tests are not initiated or tracked through our pathology department.

In summary, the multidisciplinary oncology PMed programmatic efforts resulted in improved physicians' understanding of the clinical utility of molecular testing, and specifically increased adoption of a PMed approach ultimately providing benefit to patients. We found the physicians valued the operational and clinical decision support available to them to help take care of their patients with cancer. As the applications for genomic medicine increase, the need for physician support will only increase. We have

been flexible and collaborative to best serve our patients and medical staff. We propose our model for a coordinated PMed program as a service. Other community hospitals could use a similar system to use genomic information and educational efforts to better serve their patients in their communities.

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