Clinical Sequencing at the UW Collagen Diagnostic Laboratory: An institutional experience with reimbursement and competing commercial services

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A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2020

Committee:

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Program Authorized to Offer Degree:

Public Health Genetics

University of Washington

Abstract

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Background: Next-generation sequencing (NGS) technologies pose unique challenges to traditional coverage and reimbursement mechanisms for clinical diagnostic testing. Despite rapid clinical implementation and growing test availability, reimbursement remains a substantial barrier to patient access and laboratory sustainability. The financial sustainability of academic laboratories may be further challenged by the growth in commercial genetic testing laboratories. Few reimbursement analyses on the financial sustainability of germline NGS testing have been reported outside of oncology settings. Germline NGS has a key role in genetic diagnosis for rare disorders, especially heritable connective tissue disorders (HCTDs). Rare disease patients may face additional reimbursement barriers. Given the uncertain reimbursement environment and evolving genetic testing landscape, we examined the institutional experience of an academic precision diagnostics laboratory specializing in HCTD with NGS test reimbursement and competing commercial services.

Objective: The aims of this study are to assess payer distribution and average reimbursement for NGS tests, identify residual cost to insured patients, assess utilization of competing commercial services, and determine where the burden of cost for genetic testing currently lies in the academic environment.

Methods: A retrospective review of administrative claims for NGS testing performed by the Collagen Diagnostic Laboratory (CDL) was undertaken. Evaluation of reimbursement was performed with use of CPT codes 81410 and 81479 and reported for two patient cohorts, one billed through UW Physicians (UWP) and the other through UW Medical Center (UWMC). Laboratory utilization data for HCTD patients referred for genetic testing at the UWMC Genetic Medicine Clinic were examined to see the percentage of patients who chose to utilize outside laboratory testing services. Cost burden and financial sustainability were assessed using the fraction of remaining charges to patients and the CDL after insurer reimbursement.

Results: On average, reimbursement from third-party payers using the 81410 CPT code was at 22% (Commercial, 25%; Medicare, 0%; Medicaid, 31%; HIX, 12%) of total charges for UWP claims and 27% (Commercial, 37%; Medicare, 0%; Medicaid, 1%) for UWMC. Using CPT 81479, reimbursement was at 28% (Commercial, 32%; Medicare, 0%; Medicaid, 19%) of total charges for UWP and 33% (Commercial, 41%; Medicare, 0%; Medicaid, 6%; HIX, 0%) for UWMC. Use of commercial laboratory services was negligible. Insured patients were responsible for 26% and 15% of the respective codes' charges billed by UWP. The CDL received no payment for 52% and 58% of claims billed by UWMC for 81410 and 81479, respectively, and 20% and 30% of claims billed by UWP, considering patient contributions as well.

Conclusion: Reimbursement was inconsistent and poor, with substantial variability by payer and billing agent. Billing management played a key role in payment variation. Burden of sequencing costs often fell to the CDL, which may be indicative of the greater academic sequencing environment. Human error in the reimbursement process at the institutional level after test charge submission has significant implications for the accessibility of genomic sequencing.

INTRODUCTION

Advances in next-generation sequencing (NGS) technologies and associated clinical utility evidence have facilitated the rapid adoption of genomic sequencing into clinical practice. Given the accelerated speeds, increased throughput, and reduced costs of NGS technologies, the genetic testing landscape is evolving from single-gene tests towards complex multigene sequencing.[1] As an essential tool for evaluating rare disorders, NGS-based assays play a critical role in genetic diagnosis and gene discovery for heritable connective tissue disorders (HCTD). The use of NGS-based diagnostics in HCTD for causal variant detection can improve diagnostic sensitivity and genetic discovery, and genetic testing through NGS is often used to categorize specific types of HCTD, given the overlapping features of such disorders.[2–5] Moreover, improved elucidation of variants in HCTD patients and shorter time to diagnosis, reducing the duration of a diagnostic odyssey, can allow for better treatment optimization and drive personalization of care.

Payment for genetic testing is one of the greatest issues facing the advancement of genomic medicine.[6] Despite rapid clinical implementation, growing test availability, and more than a 100,000-fold drop in the production cost of sequencing,[7] financial barriers continue to limit the scope and availability of clinical genomics as a field of medicine. NGS technologies pose unique challenges to coverage and reimbursement mechanisms, and NGS-based diagnostics face an uncertain coding and reimbursement environment.[6,8–13] Rare disease settings may pose additional reimbursement barriers that include the need for preauthorization; unfamiliarity with the genetic conditions due to limited medical specialties represented within health insurers; a resistance to approval by insurers for tests that may not align with internal assessment evidentiary thresholds; limited availability of cost information; and uncertainty about residual cost to the insured.

Reimbursement is critical to support patient access, laboratory sustainability, and the advancement of clinical genomics. Disparate access to and use of genetic services are a growing public health concern, and issues of cost and insurance have been emphasized as key contributors to variable uptake as well as a concern to patient outcomes across clinical indications.[14,15] Third-party coverage plays a significant role in the adoption of genetic testing as well as patients' desire to undergo NGS testing, given that high out-of-pocket costs can result in test cancellations.[14,16,17] Reimbursement is also coupled with the financial sustainability of

genetic testing laboratories and clinical genomics as a field of medicine. The continued provision of services relies on the receipt of appropriate revenue to account for the cost and value of service rendered; if financial gaps exist, this warrants further investigation as administrative costs may be influenced by reimbursement.

The shift from academic laboratories with expertise in specific genes to commercial laboratories[18] has further implications for NGS test accessibility and the financial sustainability of academic laboratories. The genetic testing landscape is experiencing aggressive growth in commercial laboratories, driven by marketing and price cutting. As commercial laboratories' volumes increase, they are increasingly automating interpretations, for which the chosen processes may lack the comprehensiveness and depth of resolution offered by academic laboratories. Commercial laboratories offer the impression that their low cost is a financial boon to patients, but for the insured patient, it may add to medical costs given that a policy has already been paid for. The new spending also puts additional money into medical care, which benefits the insurer even more, given what they would otherwise pay. In addition, academic laboratories are the pipelines for training the next generation of laboratory directors and personnel. Commercial laboratories may thus divert funds out of these pipelines and the medical system.

To date, few reimbursement analyses have been published on NGS-based diagnostics.[12,19–24] Reimbursement evidence is needed, especially with the evolving genetic testing landscape, changes to the laboratory industry, and overall impact of reimbursement on patient access and laboratory sustainability. Most of the literature-to-date is specific to molecular oncology practices and somatic tumor profiling. Reimbursement is frequently described as poor and inconsistent, with lowest payments, if any, recorded from government payers.[20,22–25] Moreover, NGS testing with clinically actionable results has been associated with lower reimbursement,[21] indicating that advances in genomics are outpacing coverage and reimbursement mechanisms and policies. In sum, extant evidence on the financial sustainability of germline NGS diagnostics is limited and suggests an uncertain reimbursement environment.

To better understand the uncertainty within the reimbursement environment, it is necessary to document evidence and trends of reimbursement for NGS diagnostics. This is of increasing

importance given recent policy and legislative changes affecting molecular diagnostic coding, coverage, and pricing, which are the three components of reimbursement. Briefly, the American Medical Association introduced new current procedural terminology (CPT) code sets for genomic sequencing procedures; the Centers for Medicare and Medicaid Services (CMS) developed its first NGS-specific national coverage determination; and implementation of the Protecting Access to Medicare Act changed the pricing of laboratory services and how certain laboratory tests are assigned codes.[6] Furthermore, the COVID-19 pandemic has brought national attention to current issues with the regulatory framework governing diagnostics, ushering in renewed efforts to reform existing regulations and address FDA's historic policy of LDT enforcement discretion, which has challenged NGS coverage development. The policy environment matters greatly for public health given its influence on patient access in the context of reimbursement. Its dynamic nature increases the necessity of ongoing reimbursement analyses.

The Collagen Diagnostic Laboratory (CDL) at the University of Washington is a CLIA-certified clinical and research laboratory specializing in HCTD, especially osteogenesis imperfecta, the Ehlers-Danlos syndromes, and heritable vascular disorders. As a genetic testing lab within UW Medicine's Laboratory for Precision Diagnostics, the CDL provides testing and consultation for patients with suspected HCTD. Genomic tests are performed on samples derived from both internal UW Medical Center (UWMC) clinics and test orders originating elsewhere. An alternative to testing performed by the CDL for patients seen at UW Medicine is testing performed by a for-profit commercial genetic testing company. The diversion of testing to a commercial outside laboratory (OL) could potentially present a substantial diversion of funds away from the medical system since the CDL's testing costs also support the laboratory, faculty, research, quality control systems research, new test development, and training for the next generation of laboratory and clinical personnel engaged with this set of patients, among other things. In addition, while the lower costs proffered by an OL may appear to decrease the cost of medical care, this system may prove to be a false economy given that patient premiums have already been paid to insurance.

The aim of this study is to describe the CDL's institutional experience with reimbursement, identify residual cost burden to insured patients, assess utilization of competing commercial services, and determine where the cost burden of genetic testing currently lies in the academic environment. This work addresses the aforementioned lack of reimbursement analyses in the domain of testing for rare single gene mendelian disorders as distinct from heritable and somatic cancer testing. Characterizing reimbursement can help shape coverage and reimbursement decision-making, provide insights into disparities in access, and identify knowledge and policy gaps. Improving the availability of cost information will facilitate future financial discussions and contribute to cost transparency. Furthermore, providing upfront cost estimation to patients can assist financially informed decision-making. The CDL's findings may also reveal any effects of heavily discounted pricing by large commercial laboratories on the survival of academic laboratories. Data will provide critical linkages between reimbursement, academic laboratory sustainability, and the potential impact of commercial laboratories. Here we report 1) reimbursement for two cohorts of patients whose CDL testing was billed through distinct billing mechanisms, 2) insured patient-borne costs from remaining test charges, and 3) CDL versus OL testing utilization.

MATERIALS AND METHODS

A retrospective review of all NGS testing performed between January 2017 and December 2018 by the CDL was undertaken. Administrative claims and laboratory utilization data were reviewed to improve cost transparency and examine variation in reimbursement and commercial laboratory utilization for suspected heritable connective tissue disorder (HCTD) patients sequenced at the CDL drawn from three distinct data sets. The Institutional Review Board at the University of Washington waived the patient consent process owing to minimal patient risk (STUDY00009685).

CDL Testing Process and Billing

Single gene testing, multigene panel testing, and targeted mutation/genetic testing, when a mutation was already diagnosed in a family, were provided by the CDL using NGS technology (Table 1). Tests were performed on samples derived from both internal UW Medical Center (UWMC) clinics and outpatient test orders originating elsewhere. Given the high cost of the CDL's tests, and the need to have prior authorization to qualify for insurance reimbursement,

insurance preauthorization was initiated for all outpatient orders, with the exception of Medicare, for which an advance beneficiary notice (ABN) had to be submitted. Because Medicare does not provide payment levels, this need created uncertainty for patients and often led to choice of self-pay alternatives where the cost was known through commercial laboratories.

Table 1. Genetic testing performed at the Collagen Diagnostic Laboratory

TEST NAME	PANEL	DISEASE NAME	GENE	CPT CODE
ADAMTS2 gDNA Testing		Ehlers-Danlos Syndrome type VIIC (Dermatosparaxis)	ADAMTS2	81479
ALPL gDNA Testing		Hypophosphatasia	ALPL	81479
C1S and C1R gDNA Testing		Ehlers-Danlos Syndrome type VIII (Periodontal)	C1R, C1S	81479
COL1A1 and COL1A2 gDNA Testing		Osteogenesis Imperfecta	COL1A1, COL1A2	81408 x 2
COL3A1 gDNA testing		Ehlers-Danlos Syndrome type IV (Vascular EDS)	COL3A1	81479
COL4A1 and COL4A2 gDNA Testing		Vascular disease	COL4A1, COL4A2	81408 x 1, 81479 x 1
COL4A5 gDNA testing		Alport syndrome (X-linked)	COL4A5	81408
COL5A1 and COL5A2 gDNA Testing		Ehlers Danlos Syndrome, Classic Type (Types I and II)	COL5A1, COL5A2	81479
FBN1 gDNA Testing		Marfan syndrome	FBN1	81408
FKBP14 gDNA Testing		FKBP14-related Ehlers-Danlos Syndrome	FKBP14	81479
IFITM5 gDNA Testing		Osteogenesis Imperfecta	IFITM5	81479
PLOD1 gDNA Testing		Ehlers Danlos Syndrome type VI (Ocular-scoliotic)	PLOD1	81479
PLS3 gDNA Testing		X-Linked Osteoporosis	PLS3	81479
Alport syndrome Panel	3 gene panel	Alport syndrome	COL4A3, COL4A4, COL4A5	81408 x 2, 81407 x 1
Arterial Aneurysm Panel	25 gene panel	Familial Aneurysm, Marfan Syndrome, Ehlers-Danlos Syndrome type IV	ACTA2, BGN, CBS, COL1A1, COL3A1, FBN1, FBN2, FOXE3, LOX, MAT2A, MFAP5, MYH11, MYLK, NOTCH1, PLOD3, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2	81410
Autosomal Dominant OI Panel	3 gene panel	Osteogenesis Imperfecta	COL1A1, COL1A2, IFITM5	81408 x 2, 81479 x 1
Caffey Disease Testing		Caffey Disease, Infantile Cortical Hyperostosis	COL1A1	81403
Classical and Vascular Ehlers-Danlos Syndrome Panel	3 gene panel	Ehlers Danlos Syndrome, Classic Type (Types I and II); Vascular Ehlers-Danlos Syndrome (Type IV)	COL3A1, COL5A1, COL5A2	81479
Complex EDS-like Disorders	6 gene panel	Complex EDS-like Disorders	B3GALT6, B3GAT3, B4GALT7, CHST14, CHST3, XYLT1	81479
Comprehensive EDS Panel	14 gene panel	Ehlers-Danlos Syndrome	ADAMTS2, ATP7A, C1R, C1S, CHST14, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, FKBP14, FLNA, PLOD1, SLC39A13	81408 x 2, 81479
Cutis Laxa Panel	13 gene panel	Cutis Laxa	ALDH18A1, ATP6V1A, ATP6V1E1, ATP6VO82, ATP7A, EFEMP2, ELN, FBLN5, GORAB, LTBP4, PYCR1, RIN2, SLC2A10	81479
Deletion/Duplication Analysis			Various Genes	
Ectopia Lentis Panel	4 gene panel	Ectopia Lentis	ADAMTS10, ADAMTS17, ADAMTSL4, CBS, FBN1	81479
EDS type VII Testing		Ehlers-Danlos Syndrome type VII	COL1A1, COL1A2	81479 x 2
Marfan Syndrome and Loeys-Dietz Panel	8 gene panel	Marfan Syndrome; Loeys-Dietz Syndrome	FBN1, SMAD2, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2	81408, 81405
Maternal Cell Contamination (MCC) Studies				81265
OI and Genetic Bone Disorders Panel	33 gene panel	Osteogenesis Imperfecta and Genetic Bone Disorders	ALPL, B3GAT3, B4GALT7, BMP1, COL1A1, COL1A2, CREB3L1, CRTAP, FAM46A, FGFR3, FKBP10, GORAB, IFITM5, LRP5, MBTPS2, NBAS, P3H1/LEPRE1, P4HB, PLOD2, PLOD3, PLS3, PPIB, RUNX2, SEC24D, SERPINF1, SERPINH1, SP7/OSX, SPARC, TAPT1, TMEM38B, TNFRSF11B, WNT1, XYLT2	81408 x 2, 81479
Osteopetrosis Panel	14 gene panel	Osteopetrosis	AMER1, CA2, CLCN7, CTSK, FAM20C, FERMT3, LEMD3, LRP5, OSTM1, PLEKHM1, SNX10, TCIRG1, TNFRSF11A, TNFSF11	81479
Prenatal Testing		Known Familial Mutations, Osteogenesis Imperfecta		81479 or 81403
Stickler Syndrome Panel	6 gene panel	Stickler syndrome	COL11A1, COL11A2, COL2A1, COL9A1, COL9A2, COL9A3	81479
Targeted pre-mRNA Splicing Analysis		Connective tissue disorders	Genes expressed in fibroblasts	81479
Testing for Known Mutation/Familial Variant		All diseases	All genes	

gDNA, genomic DNA; CPT, Current Procedural Terminology; OI, Osteogenesis Imperfecta; EDS, Ehlers-Danlos Syndrome.

Billing for CDL testing occurred through either University of Washington Physicians (UWP) or UWMC, and applicable billing mechanisms depended on sample source. Testing of samples sent to the CDL from outside the UW was billed through UWP, and testing of samples from patients seen at UWMC clinics was billed through UWMC.

Data

Deidentified claims data for CDL testing were provided from UWP and UWMC billing records, respectively. All claims for services performed for suspected HCTD patients between January 2017 and December 2018 using pathology and laboratory procedure CPT codes were retrieved. Claims for dates of service between January 1, 2017, and December 31, 2018, with payment decision information at the time of writing were eligible for inclusion. Deidentified laboratory test utilization data were also collected on suspected HCTD patients seen by one of the genetic counselors at the UWMC Genetic Medicine Clinic and for which a clinical genetic test was ordered and performed during the same 24-month period. These three data sets were prepared in accordance with the Health Insurance Portability and Accountability Act (HIPAA) privacy standards and Human Subject Research requirements.

Information on insurance carrier, CPT code, service date, primary diagnosis, patient cash, insurance cash, total cash receipt, and gross fees was collected from the UWP claims data. Information on insurance carrier, CPT code, service date, charge amount, payment amount, and reason for nonpayment was collected from the UWMC claims data. For outside laboratory test utilization data, information collected from the genetic counselor included test type, laboratory, authorization status, and billing process notes. Insurance carriers were coded into the following four categories, pending each data set's payer mix: Commercial, Medicare, Medicaid, and Health Insurance Exchanges (HIX).

Reimbursement Analysis

We examined differences in reimbursement for two cohorts of patients sequenced at the CDL whose testing was billed through UWP and UWMC, two distinct billing mechanisms. Reimbursement was reviewed using current procedural terminology codes (CPT) 81410 and 81479, respectively. CPT 81410 is used to bill for the CDL's 25-gene arterial aneurysm panel

and is part of the CPT code set implemented in 2015 to bill for genomic sequencing procedures, particularly NGS. Though CPT 81479 is an unlisted molecular pathology code used for tests that do not meet the component of another code, 17 of the CDL's tests are coded using one unit of 81479 (Table 1). Because code 81479 is often stacked with other codes or double-billed for certain assays, only patients with one bill for 81479 and no other claims within the study period were included in the reimbursement analysis to ensure patient and test specificity.

Reimbursement rate, defined as the percentage of test charges paid by third-party payers, was calculated differently for the respective UWP and UWMC patient cohorts, given the different data variables provided by the respective billing agents. For UWP claims, reimbursement was calculated by dividing the total sum of obtained insurance cash by the total sum of gross fees. We acknowledge that this is not a percentage of charges agreed upon by UWP and insurers and so may underestimate the efficiency of collection by UWP although reflecting the collection by the CDL for other studies. For UWMC claims, reimbursement was calculated by dividing the total payment amount by the total charge amount. We also reported the sum total of UWP claims with $0 total cash receipts and the sum total of UWMC claims with $0 total payment amounts for each respective code. Although total cash receipts reported by UWP included both patient and insurer contributions, we could not determine whether total payment amount collected by UWMC took into account any patient cash contributions to insurance cash paid.

Using the two codes for which reimbursement was analyzed, we further sought to distinguish between the burden of residual costs to insured patients and to the CDL from tests billed through UWP. The average percentage of remaining charges that insured patients paid for was calculated by dividing the total sum of patient cash by the total sum of gross fees for codes 81410 and 81479, respectively. This average out-of-pocket percentage was then added to the average percent reimbursed by third-party payers to determine the average percent of uncollected charges from the CDL. This analysis was not performed for UWMC because the patient cash variable was not provided. However, we reviewed UWMC's billing process notes for the respective payment decision information for codes 81410 and 81479 to glean additional insights on financial sustainability.

Outside Laboratory Utilization

The percentage of UWMC Genetic Medicine Clinic patients who opted for the commercial OL or other UW Medicine laboratories' services over the CDL's was calculated using HCTD patient data collected from one of the clinic's genetic counselors.

RESULTS

Summary of Claims

From our inclusion criteria, a total of 2,976 evaluable claims were billed through UWP for the testing of 1,674 patients between 2017 and 2018 (1,636 and 1,340 claims, respectively). On average, there were two molecular pathology procedures billed per patient (mean 1.77; median 2; min 1; max 7), the majority of which were for screening for genetic alterations and diagnoses of osteogenesis imperfecta (1,460 and 333 claims, respectively). Of the 2,976 claims submitted by UWP, 18% (n=521) were billed to third-party payers (74% Commercial, n=386; 20% Medicaid, n=103; 5% Medicare, n=24; 2% HIX, n=8). There were 154 evaluable claims billed through UWMC for 99 patients sequenced in 2017 and 2018 (63 and 91 claims, respectively). On average, one procedure was billed per patient (mean 1.6; median 1; min 1; max 6). Nearly all of the claims submitted by UWMC billed third-party payers (n=152, 99%), the majority of which were commercial (78% Commercial, n=118; 18% Medicaid, n=27; 3% Medicare, n=4; 2% HIX, n=3). For reasons unknown, 21 (1%) and 17 (11%) of UWP's and UWMC's respective claims were billed at $0.

Analysis of Reimbursement by Payer

UW Physicians

Reimbursement for CPT 81410

The arterial aneurysm panel was universally billed using the CPT code 81410. A total of 35 claims using CPT code 81410 were submitted to third-party payers (Commercial, Medicaid, Medicare, or HIX) by UWP. Of these billed cases, 63% went to commercial payers, 17% to Medicaid, 14% to Medicare, and the remaining 6% to health insurance exchanges (HIX) (Figure 1A). Just under half of the billed samples (46%, n=16) received some reimbursement for this NGS panel. Reimbursement by commercial payers was provided for 10/22 tests, by Medicaid for 5/6 tests, by HIX plans for 1/2 tests, and by Medicare for 0/5 tests (Table 2). No insurance cash

was collected for a total of 19 panels (54%).The average reimbursement rate across all payer types was 22% of the total amount charged for this NGS panel: 25% for commercial payers; 31% for Medicaid; 0% for Medicare; 12% for HIX (Figure 1B). Reimbursement rates were highest for Medicaid and commercial insurers (31% and 25%, respectively) compared to 0% reimbursement from Medicare.

Table 2. UWP 81410 Reimbursement

	Commercial	Medicare	Medicaid	HIX	Total
# of patients	22	5	6	2	35
# of patients with some R	10	0	5	1	16
R if paid (mean)	25%	NA	31%	12%	22%

Reimbursement results for 35 patients with evaluable UWP claims for NGS arterial aneurysm panel testing. R, reimbursement; HIX, health insurance exchanges; UWP, University of Washington Physicians; NGS, next-generation sequencing; NA, not applicable.

Reimbursement for CPT 81479

Reimbursement experience with CPT code 81479 was examined next. A total of 115 claims were submitted to third-party payers (Commercial, Medicaid, Medicare) by UWP for testing using one 81479 unit on behalf of 115 patients with no other testing or codes billed for during the study period. The payer mix for this code was 77% Commercial, 21% Medicaid, and 3% Medicare (Figure 1C). A little more than half the submissions (53%, n=61) received some reimbursement for this code, with commercial payers providing reimbursement for 50/88 tests and Medicaid for 11/24 tests. No reimbursement was provided by Medicare for three tests, and no insurance cash was received for a total of 53 tests (46%) (Table 3). On average, third-party payers reimbursed 28% of total charges billed. Commercial payers reimbursed at the highest rate (32%), followed by Medicaid (19%) (Figure 1D). These findings were limited given that the single unit of code 81479 could not be used to distinguish which test this code referenced.

Table 3. UWP 81479 Reimbursement

	Commercial	Medicare	Medicaid	Total
# of patients	88	3	24	115
# of patients with some R	50	0	11	61
R if paid (mean)	32%	NA	19%	28%

Reimbursement results for 115 patients with evaluable UWP claims for NGS testing using code 81479. R, reimbursement; UWP, University of Washington Physicians; NGS, next-generation sequencing; NA, not applicable.

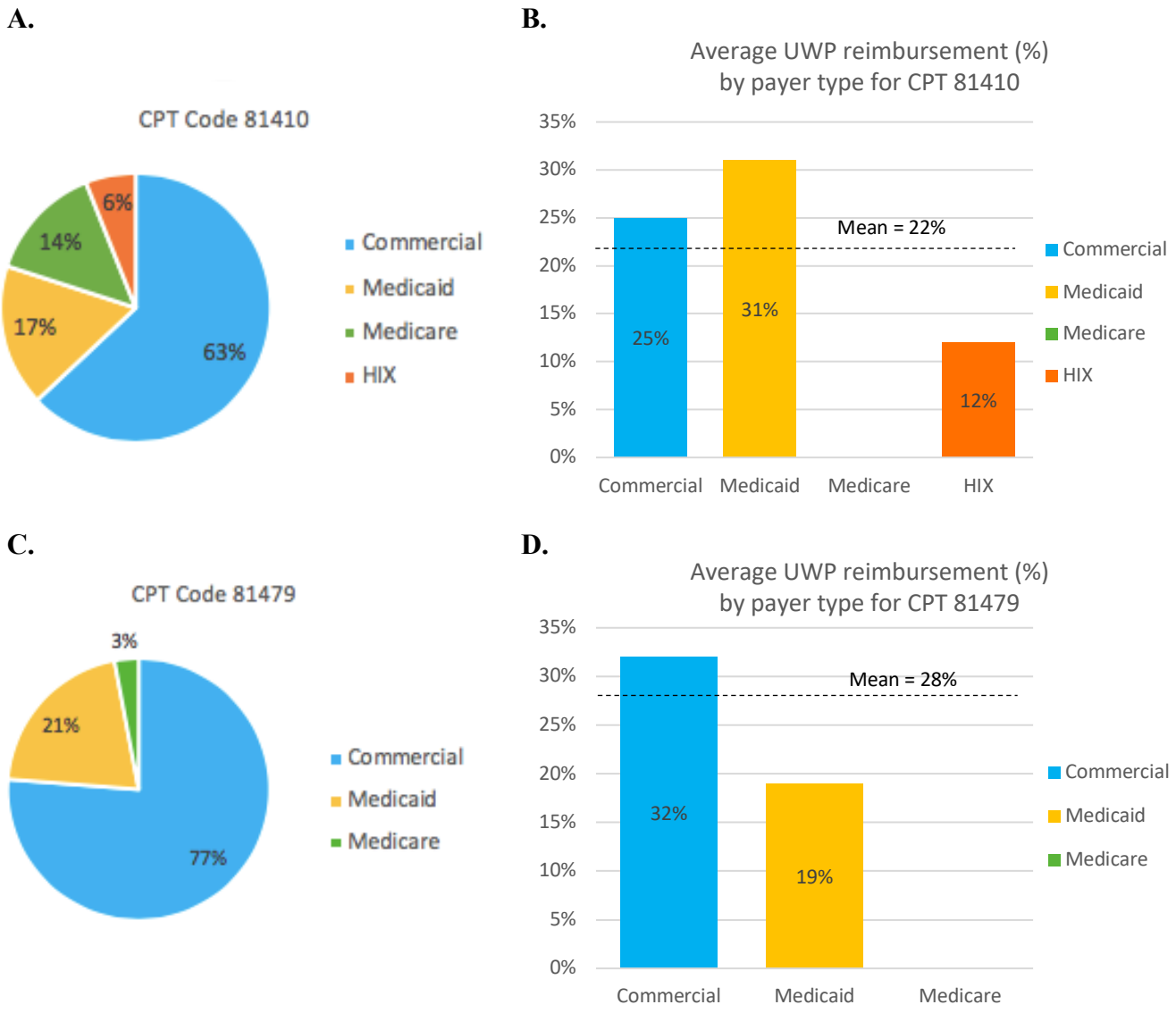

Figure 1 UWP payer distribution and average reimbursements for CPT codes 81410 and 81479. Payer mix for cases coded under 81410 (**A**) and the average reimbursement by payer type as a percentage of test fees for cases coded under the arterial aneurysm panel using 81410 (**B**). Payer distribution for single cases coded under 81479 (**C**) and average reimbursement by payer type (**D**). n=35 (**A**); n=115 (**C**). The cases included in the reimbursement analysis span 2 years. HIX, health insurance exchanges; CPT, Current Procedural Terminology; UWP, University of Washington Physicians.

Remaining Burden of Cost

Of the 521 claims billed to third-party payers by UWP using pathology and laboratory procedure codes, insured patients were responsible for an average of 15% of total charges. In addition, $0 total cash receipts from patient and/or insurance were seen in 16% (n=83) of these claims. For claims using code 81410, insured patients paid an average of 26% of the panel's charges. Given

that insurers reimbursed an average of 22% of charges, an average of 52% of the panel's charges were not collected. For insured patients with only one claim for 81479 and no other testing during the study period, patients paid for an average of 15% of test charges. Given that payers reimbursed an average of 28% of test charges using code 81479, an average of 57% of test charges was not collected by UWP for this code. Moreover, $0 total cash receipts from patient and/or insurance were seen in 20% (n=7) and 30% (n=31) of tests billed to third-party payers using 81410 and 81479, respectively. In summary, the fraction of reimbursement from patients and third-party payers summed up to an average total of 48% for 81410 and 43% for 81479 (Figure 2); more than half of charges for these codes often went uncollected, and patients were responsible for a portion of what insurers did not cover.

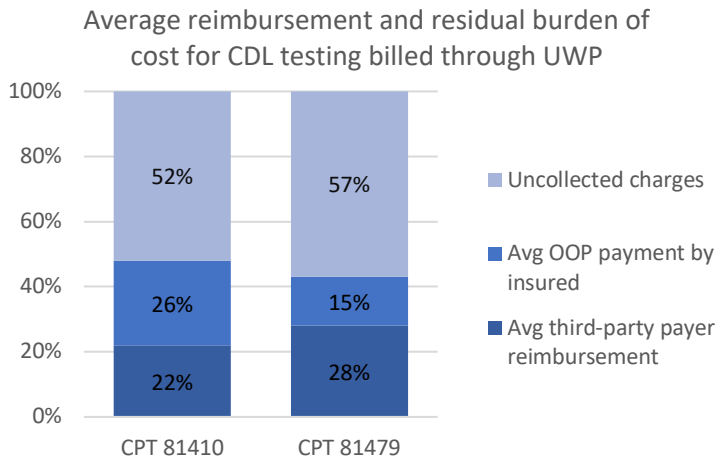

Figure 2 Distribution of residual burden of costs among the insured and the CDL for testing billed through UWP. OOP, out-of-pocket; CDL, Collagen Diagnostic Laboratory; UWP, University of Washington Physicians; Avg, average, CPT, Current Procedural Terminology.

University of Washington Medical Center

Reimbursement for CPT 81410

A total of 37 claims using CPT 81410 were billed by UWMC to third-party payers (Commercial, Medicaid, Medicare). Because the UWMC cohort with aneurysm panel testing was selected based on having procedure codes indicating one panel test of interest, 16 claims specific to four patients billed for multiple aneurysm panels were excluded from analysis. The remaining 21 claims were specific to 21 patients who each had one respective panel test. Of these 21 claims, 71% went to commercial payers, 19% to Medicaid, and the remaining 10% to Medicare (Figure 3A). Close to half of patients (48%, n=10) received some reimbursement for the panel: reimbursement by commercial payers was provided for 7/15 panels and by Medicaid for 3/4

panels. No reimbursement was provided by Medicare for two panels. A total of 11 tests (52%) had $0 payment amounts (Table 4). Review of the 21 claims billed to third-party payers using CPT 81410 showed that 27% of the panel's total charges was reimbursed on average across all payer types. Reimbursement rate was highest among commercial payers (37%), compared to only 1% for Medicaid and no reimbursement from Medicare (Figure 3B).

Table 4. UWMC 81410 Reimbursement

	Commercial	Medicare	Medicaid	Total
# of patients	15	2	4	21
# of patients with some R	7	0	3	10
R if paid (mean)	37%	NA	1%	27%

Reimbursement results for 21 patients with evaluable UWMC claims for NGS arterial aneurysm panel testing. R, reimbursement; UWMC, University of Washington Medical Center; NGS, next-generation sequencing; NA, not applicable.

Reimbursement for CPT 81479

UWMC submitted a total of 31 claims using one unit of CPT 81479 to third-party payers (Commercial, Medicaid, Medicare, HIX) on behalf of 31 respective patients with no other claims billed for during the study period. There were 17 tests for which these claims could have been billed for. Of these 31 claims, the payer mix was 74% commercial, 19% Medicaid, 3% Medicare, and 3% HIX (Figure 3C). Less than half of tests (42%, n=13) received some reimbursement, with commercial payers providing reimbursement for 11/23 tests, Medicaid for 2/6 tests, Medicare or 0/1, and HIX for 0/1 (Table 5). Of the total 31 claims charged, 18 (58%) received $0 total payments. On average, third-party payers reimbursed 33% of total charges billed for tests using one unit of 81479: 41% from commercial payers, 6% from Medicaid, and 0% from Medicare and HIX, respectively.

Table 5. UWMC 81479 Reimbursement

	Commercial	Medicare	Medicaid	HIX	Total
# of patients	23	1	6	1	31
# of patients with some R	11	0	2	0	13
R if paid (mean)	41%	NA	6%	NA	33%

Reimbursement results for 31 claims with evaluable UWMC claims for NGS testing using code 81479. R, reimbursement; UWMC, University of Washington Medical Center; NGS, next-generation sequencing; NA, not applicable.

Figure 3 UWMC payer distribution and average reimbursements for CPT codes 81410 and 81479. Payer mix for cases coded under 81410 (**A**) and the average reimbursement by payer type as a percentage of test fees for cases coded under the arterial aneurysm panel using 81410 (**B**). Payer distribution for single cases coded under 81479 (**C**) and average reimbursement by payer type (**D**). n=21 (**A**); n=31 (**C**). The cases included in the reimbursement analysis span 2 years. HIX, health insurance exchanges; CPT, Current Procedural Terminology; UWMC, University of Washington Medical Center.

Remaining Burden of Cost

Billing process notes with payment decision information from UWMC were available for 10 of the 21 claims using code 81410, and 14 of the 31 claims using code 81479, from the reimbursement analysis. Review of the respective notes for codes 81410 and 81479 billed to third-party payers showed that claims with $0 payments collected were either denied, written off, bundled with other claims, or billed at $0 for reasons unknown. For 81410, five claims were denied (n=3, not proven effective; n=1, no preauthorization; n=1, experimental), three were

written off (n=1, late charge; n=2, insufficient documentation), and the remaining two were bundled to an outpatient visit (with clinic visit code G0463) as a possible result of payer error. For the 14 claims using 81479, five were denied (n=2, not medically necessary; n=2, deemed experimental; n=1, missing record per payer error), three were written off as late charges, one was not covered by Medicare, and the remaining five were unknown as to why billed at $0. In summary, residual cost burden resulted from issues regarding coverage and billing errors.

Evaluation of Outside Laboratory Test Utilization

Among the 82 connective tissue disorder patients evaluated by the genetic counselor at the UWMC Genetic Medicine Clinic and referred for testing during the study period, 75 (91%) underwent genetic testing. The remaining 9% (n=7) who did not have testing performed either had insurance authorization denied (n=6) or authorization granted but were out-of-network (n=1). Among these 75 patients, 91% (n=68) had testing performed by the CDL, 3% (n=2) by the commercial outside laboratory, 5% (n=4) by the Northwest Clinical Genomics Laboratory, and 1% (n=1) by UW Cytology.

DISCUSSION

Reimbursement, Cost Burden, and Outside Laboratory Utilization

This study provides an analysis of the reimbursement experience for one institutional academic precision diagnostics laboratory. We examined reimbursement levels from different payers, the residual cost to insured patients, determined the burden of payments at different locations along the billing pathway, and assessed the use of competing commercial services over a 24-month period. We found that reimbursement for CPT codes 81410 and 81479 was variable and insufficient to match the CDL's testing charges. Our study analyses show similarly low rates of payments relative to other published reimbursement data on NGS testing for both orphan and nonorphan disease settings.[12,19,21–25] Such rates may limit the availability and financial sustainability of NGS, particularly multigene panels, in clinical practice, and threaten the existence of small laboratories that carry the burden of training the next generation of laboratory professionals.

Among payers, we found that Medicaid reimbursed at the highest rate (31%) for 81410 claims billed by UWP but almost negligible amounts for the UWMC claims, at 1%. This payment variability by billing system identifies the opaque nature of hospital-payer contracting as a critical component in the CDL's billing pipeline that can influence patient access, as well as the laboratory's financial sustainability. If reimbursement to the same institution differs because different billing pathways operate under different contractual arrangements, efforts should be made to standardize contracts and limit them to one format, regardless of what pathway billing traverses within the institution. Medicare provided no reimbursement for either code analyzed across both of the CDL's billing pathways. This is consistent with other published findings of poor to no reimbursement from government entities.[22–25] The lack of reimbursement by Medicare may be due to the slower evolution of public coverage frameworks compared to private coverage policy generation. Despite an increasing number of private payer policies covering multigene tests,[16] CMS did not finalize its first national coverage determination (NCD) on NGS testing until March of 2018 for patients with advanced cancer meeting certain criteria.[26] Though revised in 2020 to expand coverage for both somatic and germline mutations, this NCD remains the only national coverage policy for NGS testing, and is restricted to testing related to cancer. In the CDL's experience, reimbursement across third-party payers for both codes is poor.

The CDL and its patients are faced with substantial residual burdens of cost. Claims processing error could explain why our UWP data show that patients were not responsible for the majority of remaining charges after insurer reimbursement. The discrepancies in collected amounts may be due to late billing, insufficient documentation, and incorrect attribution to contractual allowance. Of great concern is the large amount of claims identified that received zero payment: 52% and 58% of claims billed by UWMC for 81410 and 81479, respectively, and 20% and 30% of claims billed by UWP. The attribution of nonpayment to denials, write-offs, possible payer error, and reasons unknown shows that billing management plays a substantial role in payment variation, likely due to the complexity of follow-up often required at the payer-billing system interface and lack of institutionalized mechanisms for such processes to address payment issues. The unknown reasons and denials due to medically unnecessary determinations are particularly noteworthy in revealing the role of human error at the payor-billing system interface. Such issues should be raised and dealt with during the preauthorization stage, where coverage justification

and initial appeals are managed upfront, yet all of the CDL's claims reviewed had received prior authorization. For all claims submitted by CDL for pathology and laboratory procedure codes during the study period, 11% of UWMC's claims were billed at $0, compared to almost none of UWP's claims (1%). This further demonstrates the error-prone nature of claims processing while also revealing variability in billing management by billing pathway. Billing directed by two different systems introduces additional complexity to reimbursement. Moreover, the CDL's experience illustrates how preauthorization and coverage do not guarantee reimbursement.

Our data also show almost no OL service utilization for a select HCTD patient cohort. Given our reimbursement findings for the CDL, other factors are arguably a greater threat to the CDL's financial sustainability than competing commercial services. However, selective sampling based on genetic counselor and clinical site as well as limitations in sample size prevent further inferences to be drawn. Commercial genetic testing companies will likely continue to play an increased role in the development and delivery of genetic services,[27] and research should further examine their impact on academic genetic testing laboratories.

Billing Complexity

We found that the CDL's financial sustainability and patient access to testing may be a function of the complex billing workflow after test charges are submitted by the CDL to the billing agent (UWP and UWMC), the efficiency of which can vary by billing agent. This is a critical finding because payments to the CDL, and often other molecular diagnostic laboratories, are a function of contractual arrangements with billing systems, hospital-payer contracts, payer coverage policies, and efficient revenue cycle management. These leverage points introduce additional degrees of complexity to billing processes. Thus, as coding and coverage policies continue to evolve, efficient hospital and laboratory billing infrastructure are still needed to achieve reimbursement.

Our reimbursement assessment reveals various points throughout the CDL's billing workflow that can introduce variability and challenges to reimbursement. The preauthorization process for sequencing is costly, time-consuming, and operates in the context of a "first say no" culture by insurers that leads to the need to re-submit many requests. Throughout this initial stage in the

billing pathway, claims processing and coverage justification pose a substantial administrative burden, which is likely further influenced by the need to accommodate heterogeneous and evolving policy requirements for NGS coverage[28] as well as the high degree of variability as to how payers assess multigene test coverage.[16] Given the potential impact of billing complexity on claims management and reimbursement, due diligence is required to address any human and non-human errors throughout preauthorization and billing processes more broadly. Specialized billing workflows and tailored processes specific to clinical sequencing are needed.[19,28]

Regulatory Framework and Coding Practices

The problem of billing management for testing by the CDL is of particular concern given the additional reimbursement challenges previously identified for high-cost NGS technologies.[8] For the CDL, regulatory uncertainty and evolving coding practices are particularly noteworthy to discuss.

Looking at the regulatory environment, the FDA has historically exercised enforcement discretion towards all LDTs (Laboratory Developed Tests), a category under which the CDL's tests fall given their development and use within a single laboratory. Many NGS tests are LDTs and therefore not cleared or approved by FDA but rather receive quality approvals via CMS's Clinical Laboratory Improvement Amendments (CLIA) program.[29] This can complicate payer coverage determinations; FDA clearance or approval is a specific requirement for national coverage under the Medicare national coverage determination for NGS diagnostics, and many private insurance payers model their own coverage determinations from CMS policies and procedures.[26,30] Therefore, reimbursement barriers identified in this study may derive from the current genetic testing regulatory environment.[9] Notably, draft legislation affecting how LDTs are to be regulated has been introduced,[31] and recent efforts have been made by FDA to accelerate the establishment of a regulatory approach for NGS testing.[32] Moreover, the COVID-19 pandemic has brought increasing national attention to diagnostics regulation and the LDT oversight debate.[33,34] This dynamic regulatory environment will likely continue to introduce coverage and reimbursement uncertainty for NGS diagnostics. It will be increasingly important to monitor any subsequent changes to the regulatory framework and their influence on the CDL and other academic genetic testing laboratories' reimbursement mechanisms.

Evolving and complex molecular coding practices for NGS procedures may present an additional barrier to reimbursement.[1,12] Both of the codes examined in this paper are part of the AMA's more recent iterations of CPT codes introduced to the molecular code set, the evolution of which has been described in the literature. [9,12,13] Briefly, concerns with coding specificity and transparency helped bring about modifications to the existing CPT structure to accommodate molecular pathology developments and commonly used NGS-based assays; a two-tiered molecular pathology code set was introduced in 2012 to replace code-stacking with methodology-based codes, followed by new codes in 2015 under Genomic Sequencing Procedures (GSP) to address the needs of NGS testing. The miscellaneous code 81479 had been introduced to the CPT code set in 2013 under tier-2 molecular pathology procedures, and CPT 81410 is a GSP code. While other coding policies have been implemented, these are beyond the scope of this paper but introduce additional coding complexities. Though the introduction of GSPs facilitated the reimbursement potential for NGS testing, the denial for any claim submitted with a GSP code was almost certain upon the code set's implementation.[13] While there has been an increase in the use of such coding over time,[1] molecular coding changes and the adoption of GSP codes have been found to result in substantial decreases in reimbursement as a result of decreased valuation and increased denials of coverage.[12] Coverage policies for new codes have struggled to keep pace with the clinical adoption of novel diagnostics,[23] and lower payments have also been reported for tests using NGS codes compared to non-NGS codes.[19] This is something to consider regarding our finding of lower reimbursement for tests billed using code 81410 compared to 81479 by respective billing agent, despite the nonspecific nature of 81479 and its lack of granularity for claims processing. We hypothesize that evolving molecular coding models and GSP implementation could have influenced the CDL's reimbursement, and future research should compare reimbursement for specific NGS tests before and after the CDL's transition to certain molecular pathology and GSP codes for billing.

The CDL's coding system illustrates the continued complexity of coding methodologies for NGS testing. Many of the CDL's tests lack procedure-specific codes and are either coded using the unlisted CPT 81479 individually, double-coded, or stacked with other codes for billing. Despite using the same code(s), each of these tests can differ by gene number and size, platform, type of variant(s) tested, interpretative analysis, reporting practices, and subsequent courses of action.

These CDL tests that don't meet the specific components of another GSP or molecular pathology code indicate that current coding methodologies arguably remain insufficient to identify genetic tests and efficiently communicate medical necessity to payers. Lack of coding granularity may therefore impose additional challenges for the CDL's preauthorization and claims adjudication processes by adding to the administrative burden of coverage justification, claims processing, and follow-up at the UWP and UWMC level. We consider that coding practices are a likely contributing factor to the CDL's reimbursement uncertainty and inconsistency. More procedure-specific codes for NGS tests are needed, but the CDL and other laboratories should consider the demonstrated financial impact that molecular coding changes can have on reimbursement, as Hsiao et al demonstrated.[12]

Limitations

Coding practices are not just a reimbursement issue but a hindrance to research. The CDL's reimbursement assessment was particularly challenged by the lack of procedure-specific codes and resulting inadequacy of claims data for test identification. Due to this limitation, coding specificity was the key reason for selecting the arterial aneurysm panel for analysis. The panel-specific reimbursement findings for code 81410 were much more informative compared to the test-agnostic findings of CPT 81479, from which we were unable to distinguish among different NGS tests. In fact, some analyses of clinical genomics reimbursement have explicitly excluded CPT 81479 due to the nonspecific nature of the code and high variability in payments.[19] Regardless of its limitations, we described reimbursement for CPT 81479 because the code represented the greatest number of NGS tests offered by the CDL. Despite revisions to the molecular code set, poor coding specificity remains a substantial barrier to research efforts examining the utilization and reimbursement of NGS tests as well as quality improvement initiatives. Coding complexity has significant implications for what we know and think about the accessibility of genomic sequencing in the academic environment. There is an ongoing need to address these coding difficulties given their limitations for research.

This study has several additional limitations. Because this claims review is retrospective and the data de-identified prior to access, potential sources of error may include problems with individual records, such as missing data or errors in data entry. The retrospective nature of this

study also limits our understanding of the current reimbursement environment for NGS-based tests. Moreover, the study was not able to assess influences to and changes in reimbursement, given its descriptive, cross-sectional design. As a result of differing data variables provided by the respective billing agents, comparisons made between reimbursements for UWP and UWMC claims are limited by the different ways in which reimbursement was calculated. Our reimbursement findings may further underestimate the efficiency of collection by UWP given that reimbursement was not defined as a percentage of charges agreed upon by UWP and insurers but rather a percentage of gross fees. Additionally, because the CDL offers a variety of different genetics tests, some of which do not use NGS but rather Sanger sequencing or other testing methodologies, the generalizability of our findings is limited. An additional limitation is that the CDL does not provide whole genome or exome sequencing, which further restricts the generalizability of conclusions to certain NGS-based tests. Findings are also specific to a small population of suspected HCTD patients.

CONCLUSION

As NGS technologies play an increasing role in precision medicine, this assessment provides a view of the reimbursement landscape for NGS diagnostics for HCTD. Such a snapshot is necessary given the evolving policy and regulatory landscape; foundational data are required for subsequent evaluations assessing whether coverage and reimbursement mechanisms are keeping pace. This institutional study is a step in the direction of better understanding reimbursement for clinical NGS diagnostics and the financial sustainability of academic genetic testing laboratories. The recognition of human error in the process at institutional levels after charges are submitted should not be ignored, and standardized mechanisms to control that variable should be instituted.

Acknowledgements

I owe tremendous gratitude to my committee members, Peter Byers and Paul Fishman. I am incredibly thankful for their thoughtful and encouraging guidance, limitless patience, and invaluable mentorship. I would also like to acknowledge Lynn Davis, Kim Glockner, Sean Conner, and Lauren Puryear for assistance with collection of billing and laboratory utilization data, and Ragan Hart for helpful comments and discussion regarding the manuscript.

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