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Agenda

- **Selected Posters from PLUGS Summit 2019**
  - **Lee Zellmer, MS, CGC – Children's Mercy Hospital**
    Cerner PowerForms as a novel technique for reducing ordering errors in complex genetic testing.
  - **Nicole Collier, MHSc. Dayton Children's Hospital**
    Using Laboratory Stewardship Initiatives to Guide Best Practice Ordering for Celiac Screening of Pediatric Patients.
  - **Lauren Moissey, MS, CGC. Blueprint Genetics**
    Improved Mapping Quality and Coverage in Highly Homologous PKD1 Gene Enable High Diagnostic Yield in ADPKD.
  - **Hsuan-Chieh Liao, PhD. Department of Laboratories, Seattle Children's Hospital**
    A retrospective analysis of laboratory send-out test ordered by naturopathic doctors for pediatric patients.
  - **Erin Schuler, PhD. University of Kentucky**
    Evaluation of a Urine Drug Screening Strategy in the Emergency Department (ED): A Data-driven Approach.
  - **Dustin Bosch, MD, PhD. University of Washington School of Medicine**
    Correlation of Non-invasive Helicobacter pylori Tests and Gastric Biopsies in Clinical Practice: Superior Sensitivity of Serology.
  - **Jessica Shank, CGC. Ann and Robert H Lurie Children's Hospital of Chicago**
    Implementation of a Time Tracking System within a Laboratory Utilization Management Program.
- **Save the Date for Midwest Summit**
- **PLUGS on the road**
- **Choosing Wisely Committee**

Cerner PowerForms as a novel technique for reducing ordering errors in complex genetic testing

Zellmer LA[1,2], Knipp BS[3], Burt KJ[3], Faller DA[1,2], Farrow E[1], Thiffault I[1,2], Saunders CJ[1,2], Guest E[4], Farooqi MS[1,2]

[1]Center for Pediatric Genomic Medicine, [2]Dept. of Pathology and Laboratory Medicine, [3]Dept. of Medical Informatics, [4]Dept. of Hematology/Oncology/BMT, Children's Mercy Kansas City, Kansas City, Mo.

Introduction

Test ordering errors have been demonstrated to be a frequent cause of poor laboratory test utilization and are a key target for laboratory stewardship efforts. In addition, commonly used electronic medical record (EMR) platforms demonstrate a lack of conditionality which becomes increasingly burdensome as genetic testing becomes more complex. This leads to the recollection of specimens, delays in testing, and a likely decrease in patient/provider satisfaction with the genetic testing process. We present a novel technique for obtaining the proper specimens, consent, and preauthorization needed for complex genetic testing without undue burden or educational requirements for ordering providers.

Methods

The Center for Pediatric Genomic Medicine (CPGM) at Children's Mercy Hospital is planning to begin offering tumor+normal genome sequencing in July of 2019. Our test, Cancer WGS Comprehensive, involves comparing the genome sequence of neoplastic cells with the patient's germline for detection of somatic variants (individually ordered as 'Cancer WGS Somatic'), as well as germline analysis for pathogenic variants associated with inherited pediatric cancer syndromes (individually ordered as 'Cancer WGS Inherited'). Such testing requires collection of multiple sample types from the individual, depending upon the diagnosis, transplant status, and disease timepoint. In some cases, DNA from a bone marrow donor or archived tumor specimens must be procured. Furthermore, germline testing requires informed consent and family history to be obtained by a certified genetic counselor. This testing is offered for both new cancer diagnoses and relapse cases.

The CPGM staff evaluated a number of different techniques to assist providers in placing the correct number and type of orders needed for this testing, including pop up windows, flow charts, Cerner PowerPlans, Cerner PowerForms, and genetic counselor ordering assistance. Of these, the Cerner PowerForm was determined to be the most effective and least burdensome method for both clinical and laboratory staff.

Figure 1

Cerner PowerForm Design: These six questions, along with the type of encounter the order was entered on, provide the triggers for the Cerner Discern Expert rules to place a variety of orders.

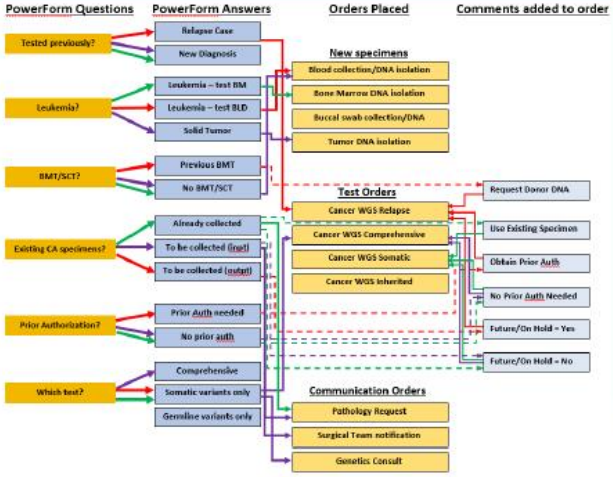
Figure 2

Examples of Cerner Discern Expert rules triggered by the PowerForm questions completed by the ordering provider. A solid line indicates an order being placed; a dashed line indicates that text is being added to an existing order

Scenario 1: A patient with relapsed leukemia who had a bone marrow transplant is being seen in the Hem/Onc clinic as an outpatient. The provider wants reanalysis of their previous Cancer WGS using a relapse specimen after insurance preauthorization is obtained.

Scenario 2: A patient with a newly discovered solid tumor is currently inpatient and biopsy is scheduled for the next day. The provider wants to evaluate for both somatic and germline variants.

Scenario 3: A patient with a new diagnosis of leukemia had a bone marrow aspirate collected the previous day and is currently inpatient. The provider wants to evaluate the genome for somatic variants only.



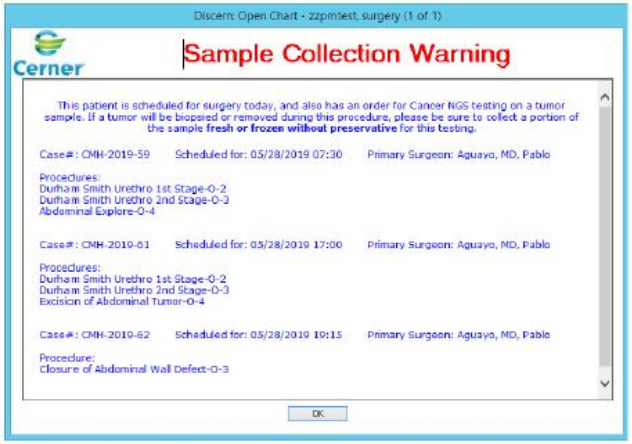
Results

A PowerForm was written with six questions (Figure 1) to be answered by the ordering provider. These questions were written in a simplified language and paired with additional text that further explained the question's intent. Each of the 168 possible combinations of answers was mapped to the group of orders necessary for that scenario (see Figure 2 for examples). A Cerner Discern Expert rule was developed that placed the appropriate orders in the patient's EMR with prepopulated order details based on the questionnaire within the PowerForm. The orders were also placed in the appropriate collection and order statuses, (i.e. collected, nurse collect, or future order status), based on the answers given and the encounter type used to complete the questionnaire.

Results, cont.

One significant challenge to genetic testing of tumors is coordinating with the pathology and surgical staff about the specimen requirements (i.e., fresh/frozen tumor rather than decalcified or preserved specimen). We developed a novel technique wherein the PowerForm triggered both an email notification to the Surgery APRN team when the order was placed, and a pop-up in the EMR when the patient's chart is opened on the day the surgery is scheduled (Figure 3).

Figure 3



Surgical team notification:
When a Cancer NGS is ordered that requires fresh/frozen tumor and a surgery has been scheduled, the Surgical APRN team receives an email when the Cancer NGS order is placed. When the Surgical team opens the patient's EMR on the day the surgery is scheduled, they receive this Cerner Discern Alert.

Discussion

As genetic testing becomes more complex, new strategies must be developed to streamline the ordering process and reduce the burden on both the ordering provider and the laboratory staff. Although associated with an up-front time commitment for the build, Cerner PowerForms are a useful tool in improving test utilization for complex genetic testing. Updates to this PowerForm are planned by the CPGM to allow for the addition of transcriptome analysis later in 2019. This will be done by adding a single question to the PowerForm, though this will, in turn, generate a large number of new ordering scenarios.

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using laboratory stewardship initiatives to guide best practice ordering for celiac screening of pediatric patients

N. Collier, L. Willis, R. Baker

dayton children's

introduction

The guidelines for screening for celiac testing have changed in recent years to discourage unnecessary panels in patients. Providers ordering testing for the patients of Dayton Children's Hospital Laboratory were using the celiac serology panel of tests to screen suspected celiac disease in a majority of cases. The Laboratory Stewardship Committee of Dayton Children's Hospital coordinated efforts with the Division of Gastroenterology and Nutrition providers to make recommendations and changes for appropriate ordering of screening tests. Using the guidelines published in an article of The American Journal of Gastroenterology[1], the Division of Gastroenterology and Nutrition providers recommended that patients should have anti-tissue transglutaminase immunoglobulin A (TTG IgA) as the preferred single test for detection of celiac disease.

january 2018

Two of the providers from the Department of Gastroenterology and Nutrition presented these recommendations and changes at the hospital's grand rounds.

november 2018

This process was reviewed in coordination with the Serology department of Dayton Children's Hospital. It was then determined that the panel which is sent to a reference lab could be performed internally for a savings to the laboratory of $325 per test. As a part of this savings initiative, the recommendation for TTG IgA only as a screening test was reiterated.

january 2017

The electronic medical record system was revised to make test names more intuitive. Additionally, an alert was added, prompting the ordering providers to choose the appropriate test based on age.

january 2016

Dayton Children's Hospital creates the Laboratory Stewardship Committee based on the PLUGS model of utilization. Initially the group is focused on applying stewardship to genetic testing.

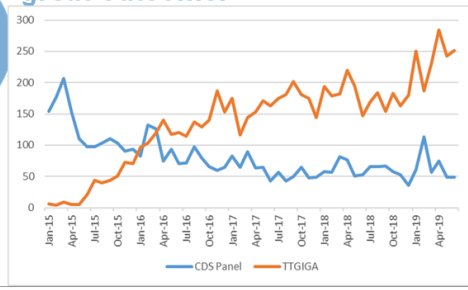
fall 2016

The Laboratory Stewardship Committee reviews volumes of the Celiac panel (CDS) compared to TTG IgA and finds that there is the potential to save each patient around $409 by ordering the correct test. This information is shared with internal and community providers by publications, lectures and outreach liaisons. These efforts included not only communicating the clinical significance, but also the financial impact to the hospital and patients.

november 2015

Using the guidelines published in an article of The American Journal of Gastroenterology, the Division of Gastroenterology and Nutrition providers recommended to staff and fellow physicians that patients over the age of two years should have anti-tissue transglutaminase immunoglobulin A (TTG IgA) as the preferred single test for detection of celiac disease.

great outcome!



Between January 2017 and January 2019:

- We reduced unnecessary testing by an average of 15%
- We insourced more testing so results are delivered faster and more reliably
- We have reduced cost to Dayton Children's Hospital laboratory by $348,850.35
- We have saved our patients $675,560.13 in charges for lab tests.

looking ahead

As testing changes evolve, it is important to continue to review testing practices. The Laboratory Stewardship Group at Dayton Children's Hospital performs an annual review of past projects as well as potential opportunities for the year ahead. This practice helps to identify testing that will benefit from quality improvement initiatives.

reference

Rubio-Tapia, Albert, Hill, Ivor D, Kelly, Ciarán P, Calderwood, Audrey H, Murray, Joseph A; ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease; The American Journal Of Gastroenterology; 2013/04/23/online; 108:656; American College of Gastroenterology; https://doi.org/10.1038/ajg.2013.79

Improved Mapping Quality and Coverage in Highly Homologous *PKD1* Gene Enable High Diagnostic Yield in ADPKD

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease. Approximately 50% of individuals with ADPKD develop end-stage renal disease (ESRD) by the age of 60 years. ADPKD is caused primarily by mutations in two genes, *PKD1* and *PKD2*, encoding polycystin 1 and 2, which are essential components of epithelial cilia. Genetic testing has become an important factor in the management of ADPKD patients and their families. However, analysis of *PKD1* is technically challenging due to its large size, high GC-content, and duplication of the first 33 exons with a high degree of homology (90-99% identity) to six nearby pseudogenes (*PKD1P1–P6*). We evaluated the diagnostic yield and performance of our in-house tailored Polycystic Kidney Disease and Cystic Kidney Disease Panels, including in total 42 genes, in an unselected cohort of patients referred for cystic kidney diseases.

Methods

Next-generation sequencing (NGS) was performed using the IDT xGEN Exome Research Panel with added custom probes and the Illumina NovaSeq 6000 platform. This assay provides improved mapping quality and coverage in many difficult-to-sequence regions, including *PKD1*, compared to other NGS methods assessed in our laboratory. Majority of the analyses (170/183) were performed as PLUS analysis that combines sequence and deletion/duplication analysis utilizing NGS data. All pathogenic or likely pathogenic variants were confirmed with an appropriate orthogonal method. Variants in the difficult-to-sequence region of *PKD1* were confirmed using Sanger sequencing with custom-designed primers.

Results

In the study cohort of 183 index patients, a genetic diagnosis was established in 54% (n=99) of cases with disease causing variants detected in 11 different genes (Table 1). In 63% and 11% of the diagnostic cases the disease causing variant was identified in *PKD1* or *PKD2*, respectively. Interestingly, 7% (n=7) of the cases had a diagnostic deletion including 4 heterozygous *HNF1B* whole gene deletions, 2 *PKD1* multiexon deletions, and 1 homozygous *NPHP1* whole gene deletion. Of all likely disease causing *PKD1* variants identified in 62 patients, 79% (n=49) were classified as pathogenic or likely pathogenic and 21% (n=13) as variants of uncertain significance (VUS favoring pathogenic) (Figure 2A). Majority of the identified *PKD1* variants were missense (40%, n=25) and nonsense (26%, n=16) variants (Figure 2B). Furthermore, 81% (n=50) of the variants were located in the duplicated region of *PKD1* (exons 1-33). A number of *PKD1* sequence variants (24%, n=15) were located in exon 15 indicating a possible mutational hotspot. In *PKD2*, a total of 11 pathogenic or likely pathogenic variants were detected that included mainly truncating variants. Additional clinical utility of the test was shown by sequencing 10 ADPKD patients with a negative test result from previous NGS-based testing (Table 2).

Table 1. Genes with diagnostic findings.

Gene	Number of cases	%
PKD1	62	63
PKD2	11	11
PKHD1	13	13
HNF1B	4	4
INVS	2	2
NPHP3	2	2
NPHP1	1	1
PRKCSH	1	1
SEC63	1	1
WDR19	1	1
PAX2	1	1

PKD1 coverage

Our panels provided mean coverage of 192x within the 42 genes. Specifically, *PKD1* provided both high mean coverage (205x) and excellent mapping quality with 99.96% of the target nucleotides covered at least 20x with a mapping quality threshold of 20 (Figure 1).

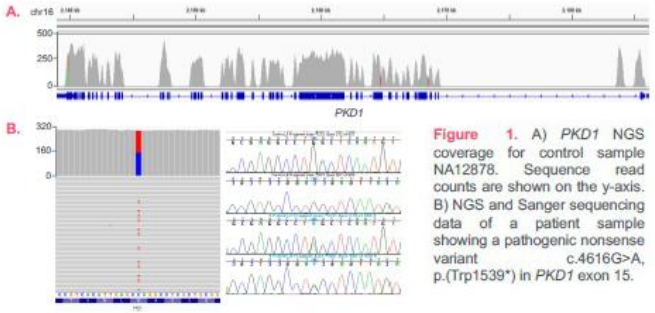

Figure 1. A) *PKD1* NGS coverage for control sample NA12878. Sequence read counts are shown on the y-axis. B) NGS and Sanger sequencing data of a patient sample showing a pathogenic nonsense variant c.4616G>A, p.(Trp1539*) in *PKD1* exon 15.

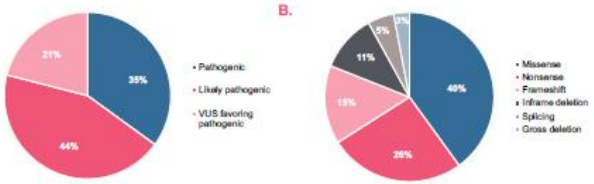

Figure 2. A) Classification and B) mutation type of the diagnostic *PKD1* variants (n=62).

Patient	Previous NGS	BpG Polycystic Kidney Disease Panel	Exon	Classification
1	Neg	c.2012C>G, p.(Ser671*)	10	LP
2	Neg	c.2180T>C, p.(Leu727Pro)	11	P
3	Neg	Negative		
4	Neg	c.2618_2621del, p.(Val873Alafs*24)	11	LP
5	Neg	c.4910T>G, p.(Val1637Gly)	15	VUS
6	Neg	c.8615T>A, p.(Ile2872Asn)	15	VUS
7	Neg	Negative		
8	Neg	c.2534T>C, p.(Leu845Ser)	11	P
9	Neg	c.5411del, p.(Gly1804Alafs*32)	15	LP
10	Neg	Negative		

Table 2. Testing of 10 ADPKD patients with a previous negative test result identified a diagnostic variant in the majority of patients.

Conclusions

- NGS-based panel testing offers good **diagnostic yield** for polycystic and cystic kidney diseases (**54%** in this series)
- Our platform demonstrates **comprehensive coverage** in difficult-to-sequence regions of *PKD1*
- Significant proportion of the identified *PKD1* variants (**81%**) were located within the duplicated region
- The method provides a cost-effective diagnostic tool for simultaneous detection of sequence and copy number variants

Blueprint Genetics

Conflict of interest statement: All authors are employed by Blueprint Genetics.

A retrospective analysis of laboratory send-out tests ordered by naturopathic doctors and general practitioners in pediatric patients

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Introduction

Naturopathy is defined as the practice of medicine for the treatment of human diseases with natural agents. It also emphasizes prevention and promotion of health through the self-healing process of the body. Tests that are performed outside of the ordering institution, send-out tests, are at increased risk of ordering the wrong or unnecessary test and misinterpreting test results. Here we evaluate the laboratory send-out tests which were ordered by naturopathic doctors (ND) and general practitioners (GP) at a tertiary pediatric care center to identify opportunities for improved laboratory stewardship.

Method

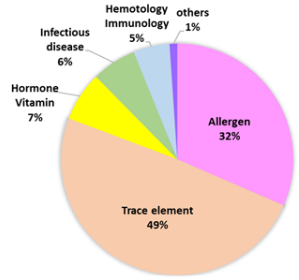
We performed a retrospective analysis from Seattle Children's laboratory send-out tests which were ordered between Jan 1, 2018 and Dec 31, 2018. We compared the tests ordered by ND with GP in our practice, by grouping the following provider specialties: internal medicine, adolescent medicine, family medicine, or pediatrics. All the requests were reviewed and categorized by test type: allergen, trace elements, hormone/vitamin, infectious disease, hematology/immunology, and others (including toxicology, oncology, genetics, and miscellaneous). Ordering frequency and abnormal rate from each category were analyzed. The abnormal rate was defined as percentage of abnormal results divided by total number of ordered tests.

Ordered tests/ provider/year	No. of ND (% of total)	tests ordered (% of total)
1-10	60 (72.3)	175 (17.0)
11-20	12 (14.5)	163 (15.8)
21-30	4 (4.8)	101 (9.8)
31-40	3 (3.6)	104 (10.1)
48	1 (1.2)	48 (4.7)
91	1 (1.2)	91 (8.8)
121	1 (1.2)	121 (11.7)
227	1 (1.2)	227 (22.0)
total	83 (100)	1030 (100)

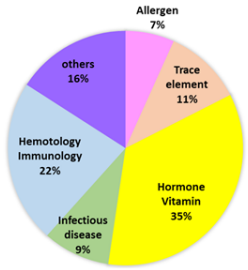
Table 1. (left)
The number of tests ordered from individual ND

Figure 1. (below)
Ordering frequency (%) from each category by ND and GP

NATUROPATHIC DOCTORS



GENERAL PRACTIONERS



Results

During the 12 month period, there were 20,312 send-out tests, 1,030 (5.1%) of them were ordered by 83 ND for 329 patients, and 3,862 (19.0%) of them were ordered by 462 GP for 2,139 patients. Four individual NDs ordered approximately half of total tests (Table 1). The most frequently ordered category by ND was trace elements (506 tests, 49.1% of total), allergen (31.5%), and hormone/vitamin (6.9%) tests (Figure 1). These three categories account 87.5% of total ordered tests. The corresponding abnormal rate was 3.3% [1], 14.6%, and 8.1%. However, once the age dependent cutoff was applied for Zinc RBC test, the abnormal rate would drop to 8.5% for trace element testing. GP ordered 416 (10.8% of total) trace element, 260 (6.7%) allergen, and 1,346 (34.9%) hormone/vitamin tests. The corresponding abnormal rate was 8.4%, 16.8%, and 21.2%, and all of them were significant higher comparing to the tests ordered by ND ($p<0.01$). Individual test and abnormal rates are shown in the Table 2 and 3.

Table 2. Trace element testing

NATUROPATHIC DOCTORS

	Number			Percentage		
Test name	Negative	Positive	Total	Negative	Positive	Total
Lead, WB	179	3 (H)	182	98.4	1.6	36.0
Zn, RBC/plasma	19	58	77	24.7	75.3	15.2
Copper	57	4	61	93.4	6.6	12.1
Aluminum	37	7 (H)	44	84.1	15.9	8.7
Mg, RBC	39	1	40	97.5	2.5	7.9
Mercury	35	0	35	100.0	0.0	6.9
Others	66	1	67	98.5	1.5	13.2
total	432	74	506	85.4	14.6	100.0

GENERAL PRACTITIONERS

	Number			Percentage		
Test name	Negative	Positive	Total	Negative	Positive	Total
Lead, WB	174	14 (H)	186	93.5	7.5	44.7
Zn, serum	29	21	74	39.2	28.4	17.8
ZPPH	38	8 (H)	46	82.6	17.4	11.1
Copper	32	7 (L)	39	82.1	17.9	9.4
Selenium	17	7 (L)	24	70.8	29.2	5.8
Fluoride	7	0	9	77.8	0.0	2.2
Others	25	13	38	65.8	34.2	9.1
total	322	70	416	77.4	16.8	100.0

WB: whole blood, Zn: zinc, Mg: Magnesium, ZPPH: Zinc protoporphyrin/Heme Ratio

Table 3. Hormone/vitamin testing

NATUROPATHIC DOCTORS

	Number			Percentage		
Test name	Negative	Positive	Total	Negative	Positive	Total
Vitamin B12	12	4	16	75.0	25.0	21.6
Progesterone	9	0	9	100.0	0.0	12.2
Folate	8	0	8	100.0	0.0	10.8
Estradiol	7	0	7	100.0	0.0	9.5
Testosterone, free + total	4	0	4	100.0	0.0	5.4
fT4 by equilibrium dialysis	4	0	4	100.0	0.0	5.4
Others	24	2	26	92.3	7.7	35.1
Total	68	6	74	91.9	8.1	100.0

GENERAL PRACTITIONERS

	Number			Percentage		
Test name	Negative	Positive	Total	Negative	Positive	Total
TSH (State newborn screen)	294	14	308	95.5	4.5	22.9
Testosterone total by LC/MS	141	121	262	53.8	46.2	19.5
Testosterone, free + Total	125	30	155	80.6	19.4	11.5
Estradiol level	120	10	130	92.3	7.7	9.7
Islet Cell autoantibody screen	35	65	100	35.0	65.0	7.4
Vitamin B12	29	7 (H)	36	80.6	19.4	2.7
Others	316	39	355	89.0	11.0	26.4
Total	1060	286	1346	78.8	21.2	100.0

Conclusion

We observed different ordering patterns between ND and GP, and the abnormal rate is significantly higher from the tests ordered by GP. These data suggest some of the tests ordered by ND lack reasonable positive predictive value or clinical significance, and could be potentially mis- or over utilized. Understanding the patterns and the variety of testing from different providers will help target interventions to improve laboratory stewardship in this area.

Reference: [1] Does Provider Specialty Matter? Variation in Serum allergen specific IgE Testing Patterns in Pediatric Patients (publish in progress)
Contact information: joyce.liao@seattlechildrens.org or jane.dickerson@seattlechildrens.org

Evaluation of a Urine Drug Screening Strategy in the Emergency Department: A Data-driven Approach

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Background

Urine drug screens (UDS) are ordered in the emergency department (ED) to evaluate patients with suspected drug-of-abuse intoxication. UDS programs that can provide reliable results with rapid turnaround time (TAT) are optimal for patients management in acute care settings. Currently, two common strategies are implemented in clinical laboratories: a one-step approach relying on mass spectrometry (MS)-based definitive assays, or a two-tier approach with initial screening by rapid immunoassays (IAs) and reflex positives to be confirmed by MS. The one-step strategy provides more reliable results; however, the suboptimal TAT delays management of critically ill patients. Thus, the IAs with rapid TAT may be a more suitable strategy for UDS in the ED.

Objective

The objective of this study is to improve utilization of urine drug screening for patients presenting to the University of Kentucky Medical Center (UKMC) Emergency Department by identifying a laboratory testing strategy with optimal clinical utility and turn around time.

Methods

- A retrospective analysis was performed on all UDS ordered by UKMC ED providers over a 6-month time period (n=3232)
  - -UDS were performed by MS and the data was evaluated to determine whether the results could be detected by our in-house IAs-based drug of abuse panel (ABUS) performed at our sister hospital ED
- A prospective comparison study between MS and IA based drug screens was also performed utilizing residual urine specimens sent from the UKMC ED for UDS (n=69)
  - -Analysis of data from the prospective study focused on determining the concordance rate and any discordant results (false positive or negative) that could potentially lead to mismanagement of ED patients
- Clinical information was acquired from patient electronic medical records (EMR)
- All data analysis was performed by the R program version 1.0.153.

Results

Table 1: Ordering volumes of UDS by location

Ordering Location	# of Orders	% of Total
University of Kentucky ED	3232	45.92%
Good Samaritan ED	463	6.58%
Clinic A	291	4.13%
Clinic B	217	3.08%
Dental Clinic	194	2.76%
Good Samaritan Hospital	138	1.96%
Family Medicine	131	1.86%
Clinic C	120	1.71%
UK Inpatient ICU	108	1.53%

Figure 1: (A) Distribution of all retrospective UDS data (B) Distribution of positive MS UDS results detectible by IAs; where IA2 represents drug detected with expanded opioid testing to include buprenorphine, fentanyl, methadone and tramadol and Others represents drugs not relevant to patient intoxication

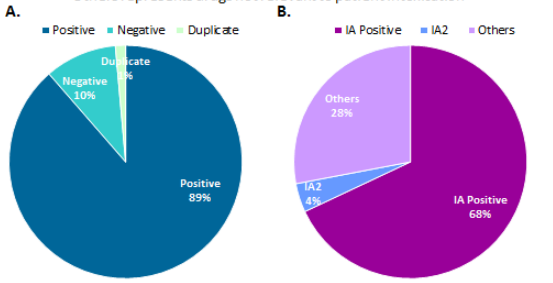
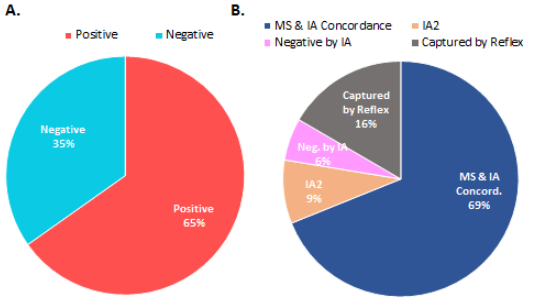


Figure 2: (A) Distribution of prospective MS data (B) Distribution of concordance between MS and IAs on prospective data



Results

Retrospective Analysis

- About 46% of the total UDS ordering is from ED (**Table 1**)
- Among the 3232 ED UDS gathered in the retrospective study (**Fig 1A**):
  - -44 were identified as duplicates and not included in the analysis
  - -326 results (10%) negative
  - -2862 results (90%) positive for any class of drug
- Among the 2862 positive results (**Fig 1B**):
  - -1950 (68%) contained drugs that are detectable by ABUS
  - -125 (4%) would be detected by IAs if we expanded the ABUS panel to include four additional opioids, including: buprenorphine, fentanyl, methadone and tramadol
  - -28% of drugs identified by MS were either not relevant to patient intoxication (e.g. caffeine) or expected based upon patient medication history, e.g. anti-depressants, anticonvulsant, anti-inflammatory, or anti-fungal drugs

Prospective Analysis

- The distribution of positive and negative results by MS is shown in **Fig 2A**. The overall agreement between MS and IA results was 78.3%
- Among MS positive results **(Fig 2B)**
  - -6% of MS were negative by IA, all of which were benzodiazepines whose concentrations were below IA cut off (<200 ng/mL)
  - -94% of all positive results would be detected by IA by expanding the IA panel and reflexing all positive results to MS confirmation

Conclusions

In this study, we evaluated the clinical utility and turn around times of two testing approaches for Urine drug screening for patients presenting to the UKMC ED. Both retrospective and prospective analyses suggest that patient management would be minimally affected by implementing a two-tier UDS approach to include an initial screen by rapid IAs with reflex to confirmation by MS, particularly if additional opioids are added to our current ABUS panel. These results emphasize the importance of selecting an appropriate UDS strategy based upon the clinical needs of patients and their healthcare providers.

References

1. Algren, D. A. and Christian, M. R. Buyer Beware: Pitfalls in Toxicology Laboratory Testing. Mo. Med. 2015, 112(3): 206–210; 2. Moeller, K.E. et al. Urine Drug Screening: Practical Guide for Clinicians. Mayo Clinic Proceedings. 2008, 83 (1), 66–76.

Correlation of Non-invasive *Helicobacter pylori* Tests and Gastric Biopsies in Clinical Practice: Superior Sensitivity of Serology

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UW Medicine Laboratory Medicine

UW Medicine Pathology

Background

Diagnosis of Helicobacter pylori gastritis can be made with tissue-based and non-invasive tests, with important implications for treatment and prevention of gastric neoplasia. Multimodal *H. pylori* diagnostic testing continues to increase. An American Society for Clinical Pathology recommendation as part of the Choosing Wisely Campaign discourages use of serology, because urea breath and stool antigen tests can distinguish active infection from past exposure.

Design

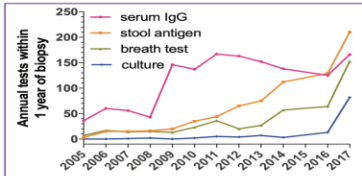
Concordance of laboratory tests with gastric biopsy was assessed retrospectively over a 12-year period at a single institution (2560 cases). Gastrointestinal pathologists reviewed 60 representative gastric biopsy cases. Diagnostic performance and cost of candidate non-invasive testing algorithms were modeled as a function of disease prevalence.

Results

Despite guidelines advocating against use of serum *H. pylori* IgG, a substantially higher sensitivity of serology (0.94) was observed in this population, compared to urea breath and stool antigen tests (0.64 and 0.61). Serum *H. pylori* IgG titer correlated with biopsy positivity, and ROC area under the curve was 0.88. Evidence for advantages of convenience and access to care with serum IgG testing included a lower test cancellation rate compared to other tests ($p < 0.001$). Interobserver variability was higher among gastrointestinal pathologists for interpretation of the histopathology (kappa 0.34) on cases with a discordant laboratory test, compared to cases with concordant lab and histopathology (kappa 0.56).

Conclusions

While *H. pylori* serology has lower specificity compared to other non-invasive tests and lacks utility in patients with prior infection, the superior sensitivity and negative predictive value in our population supports its use as a non-invasive test to rule out *H. pylori* infection. Reflexive testing with serology followed by either stool antigen or urea breath test may optimize diagnostic accuracy in low prevalence populations.



cases *n*	**2560**
biopsy positive *n* (%)	**1161 (45)**
sex % *female*	**56**
age *years (quartiles)*	**52 (39-63)**
time interval *days (quartiles)*	**63 (21-136)**

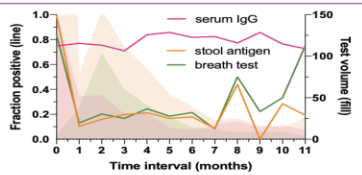
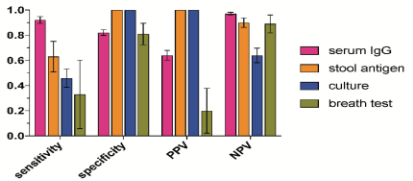


Figure 1. *Utilization of Helicobacter pylori laboratory tests in combination with bastric biopsy has increased over time.* (Left) Increasing numbers of patients had both gastric biopsy and laboratory testing for *H. pylori* over time. (Middle) Demographic data for 2560 such cases indicated a minimal female predominance. (Right) Concordance of biopsy and laboratory tests was related to time interval between the two tests. Number of non-invasive laboratory tests over time (filled curves) after an initial positive biopsy, stool antigen, or culture exhibited a peak at ~2 months, likely due to testing for confirmation of eradication. Positivity rates in non-invasive laboratory tests other than serology (lines) drop sharply at 1 month, corresponding to effective treatment.

Biopsy and lab test within 14 days

	Biopsy Result			
	totals	Positive	Equivoc.	Negative
Serum *H. pyori* IgG	443			
Positive	158	97	7	54
Equivocal	22	6	1	15
Negative	263	8	10	245
***H. pylori* stool antigen**	79			
Positive	10	10	0	0
Negative	69	6	6	57
***H. pylori* culture**	94			
Positive	21	21	0	0
Negative	73	25	4	44
Urea breath test	25			
Positive	6	1	1	4
Negative	19	2	0	17



Biopsy and lab test within 365 days

	Biopsy Result			
	totals	Positive	Equivoc.	Negative
Serum *H. pyori* IgG	1296			
Positive	424	268	43	113
Equivocal	83	12	4	67
Negative	789	17	14	758
***H. pylori* stool antigen**	551			
Positive	121	106	3	12
Negative	430	69	23	339
***H. pylori* culture**	136			
Positive	27	25	0	2
Negative	109	42	9	58
Urea breath test	261			
Positive	82	68	3	11
Negative	180	39	11	130

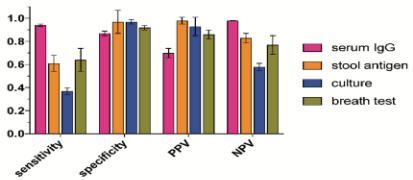
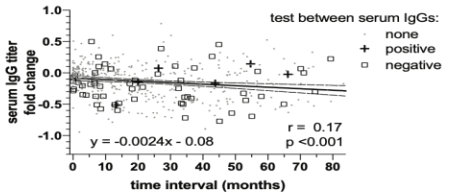


Figure 2. *Comparative performance of laboratory tests with biopsy as the reference standard revealed superior sensitivity of H. pylori serum IgG.* (Upper panel) Laboratory tests within 14 days of gastric biopsy were correlated to manually reviewed biopsy results. Sensitivity of serum IgG (0.92) was substantially higher than stool antigen (0.63), urea breath test (0.33), or H. pylori culture (0.46). However, serum IgG specificity (0.82) was lower than stool antigen or culture (1.0). Error bars represent standard error. (Lower panel) Laboratory tests within 1 year of gastric biopsy were correlated to histopathology diagnosis, excluding discordant cases explained by treatment or prior infection. A similar performance trend was observed, with serum IgG exhibiting a sensitivity advantage, while other tests were modestly more specific. Exclusion of treatment related discordance was based upon randomized chart review (see methods), and error bars represent sampling error related to chart review.



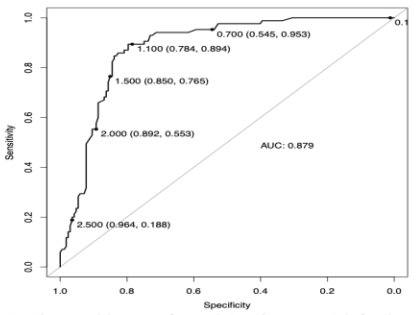
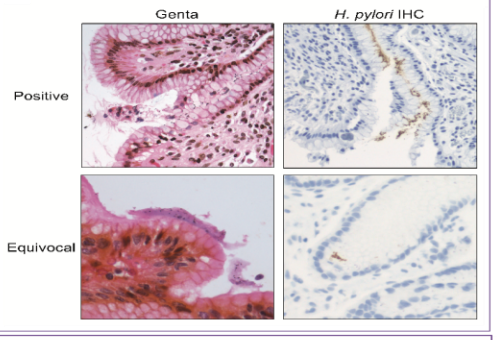


Figure 3. *H. pylori serum IgG titer correlated to biopsy result and decreased very slowly over time.* (Left) For patient with multiple *H. pylori* serum IgG tests, fold change in titer was compared to time interval between tests. The majority of patients had small or no change in titer on repeat testing, and a significant trend toward lower titer over time at a rate of -0.024 fold/month was identified. Rate of titer change was not related to evidence of eradication (negative intervening test) or evidence of persistent/recurrent infection (positive intervening test). (Right) Receiver operating characteristic analysis of *H. pylori* serum IgG titer demonstrated an area under the curve of 0.879. Points on the curve are labeled as titer cutoff (specificity, sensitivity). Cutoffs for clinical reporting were ≤0.9 negative, between 0.9 and 1.1 equivocal, and ≥1.1 positive.

	n	agreement with initial diagnosis	Fleiss kappa
overall	60	98 / 180 (54%)	0.43
concordant lab + biopsy	23	56 / 69 (81%)	0.56
discordant lab + biopsy	23	38 / 69 (55%)	0.34
equivocal biopsy	14	4 / 42 (10%)	0.04

Figure 4. *Histopathologic examination of biopsies with concurrent non-invasive laboratory testing.* (Below) H&E stained slides and either Genta stain or *H. pylori* IHC were reviewed by gastrointestinal pathologists. Representative micrographs from cases initially diagnosed as positive or equivocal are shown. Coccoid forms at the epithelial surface and immunohistochemical staining of forms lacking the classic rod shape each raise concern but are not specific for *H. pylori*. (Above) Agreement of slide review consensus with the original diagnosis was highest for cases with a concordant non-invasive *H. pylori* test and lowest for biopsies with an initial equivocal diagnosis. A similar trend was seen for interobserver concordance, reflected by Fleiss's kappa.



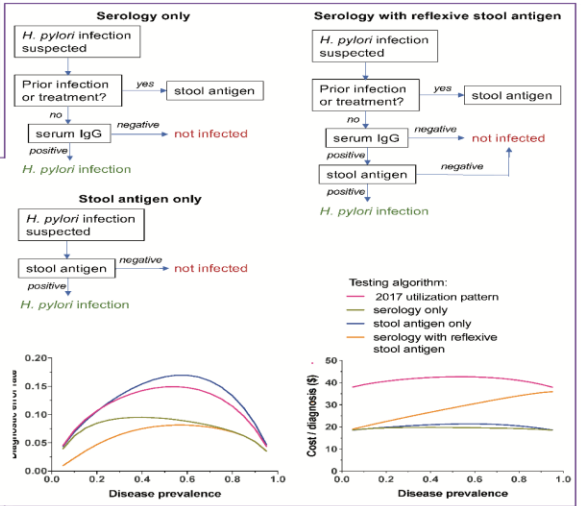


Figure 6. *Proposed testing algorithms for non-invasive diagnosis of H pylori infection.* Three candidate algorithms were modeled against disease prevalence, assuming constant sensitivity and specificity as measured in the comparison to histopathology (Figure 2). Diagnostic error rate reflects the sum of false negative and false positive rates. Cost per diagnosis is crudely modeled based on 2018 Medicare reimbursement rates for each test. Importantly, algorithms utilizing serology require exclusion of prior infection and/or treatment based on prior testing and clinical history. A serology-only algorithm exhibits better accuracy and similar cost compared to stool antigen alone. Reflexive confirmation of positive serology with stool antigen testing improves accuracy with added laboratory cost that is dependent on disease prevalence.

Implementation of a Time Tracking System within a Laboratory Utilization Management Program

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Ann & Robert H. Lurie Children's Hospital of Chicago®

Background

- Laboratory Utilization Management (LUM) program initiated in 2013
- 3 genetic counselors (GCs) with split roles in both clinical and laboratory settings

0.9 FTE LUM
0.1 FTE Cardiology

0.2 FTE LUM
0.8 FTE Oncology

0.7 FTE LUM
0.3 FTE Neurology

1.8 FTE allotted to LUM efforts

Goals of Time Tracking System

Assess time spent on:
- Test Utilization Review
- Support Services
- Long-term projects
- Hospital initiatives
- Clinical responsibilities

Monitor:
- Order volume
- Support services volume

Design

- Time spent was recorded in real-time by each GC in excel
- GCs recorded activities at the level of role and content while also recording time spent
- Counts were included when quantitative data was desired
  - Genetic testing order review
    - In-house, send-out, whole exome sequencing
  - Support Services
    - Emails, phone calls, EHR
- Start and finish time were recorded for each task
- Time-on-task was calculated based on start and finish times

Time Tracking System (TTS)

Date	Role	Content	Counts
10/4/2018	Clinic	Clinic Prep	
10/4/2018	Genetic Testing Order Review	Order Review	7
10/4/2018	Long Term Projects	Steering Committee	
10/4/2018	Email	Finance	
10/4/2018	Phone	Internal Lab Support	1
10/4/2018	Email	CPT Codes	3
10/4/2018	Email	Insurance	1
10/4/2018	Email		2

CPT Codes
Finance
Genetic Testing
Insurance
Internal Lab Support
Miscellaneous
Reference Labs
Test Logistics

- Within a particular role, content was recorded as a discrete category to further characterize the activity

Role:
Genetic testing utilization review
Support services (email, phone, EHR)
Long-term projects
Hospital initiatives
Clinic

Content:
CPT codes
Finance
Genetic testing
Insurance
Internal lab support
Miscellaneous
Reference labs
Test logistics

Content:
EMR utilization tool
Preauthorization project
Revenue cycle

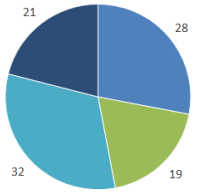
Content:
Cardiology Reimbursement
Database development
Internal website
Program development
Provider satisfaction survey
Utilization Experience
Whole Exome Sequencing

Start	Finish	Time (hh:mm)	Time-On-Task
8:30	9:45	01:15	75
10:00	11:00	01:00	60
11:00	11:20	00:20	20
11:20	13:00	01:40	100

Review of the TTS data showed that of total time, 73% was spent on LUM roles while 27% was spent on clinical tasks yielding a total contribution of 2.2 FTE compared to the allotted 1.8 FTE.

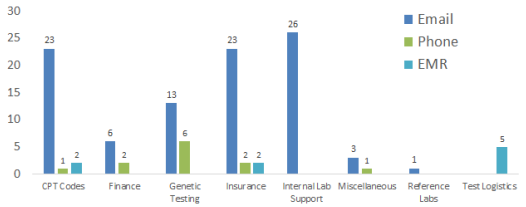
Results

LUM TIME SPENT PER ROLE (%)



Genetic Testing Order Review Metrics
13 orders reviewed daily (r. 3-27)
23 minutes spent per order (r. 5-59)

SUPPORT SERVICE REQUESTS: VOLUME BY MODALITY
DATA FROM AUGUST 2018



The LUM team received 385 requests for support services during fiscal year 2018, the majority of which (85%) were by email.

Utility of Findings

Benefits of a TTS	Barriers to a TTS
Time-on-task data can help manage expectations for responsibilities	Time investment required up front for design, user training, and maintenance
Real-time data can be generated and tailored to needs as they arise	Use may be challenging when burden of work is already high
Volume tracking can be incorporated in records	Consistency among users critical for data utility

Time-on-task data has been used for a variety of program operations
- Resource allocation
- Short-term leave planning
- Diverted inquiries better suited for other departments
- Advocacy for additional genetic counselor support

While development and utilization of a TTS can be challenging, data obtained can shed light on resource allocation and needs which can ultimately increase efficiencies and employee engagement

SAVE THE DATE

PLUGS® Midwest Regional Summit 2019

November 15th, 2019
Minneapolis, Minnesota

Presented in partnership with
ARUP Laboratories & HealthPartners

~ AGENDA ~

- **Lab Test Stewardship: Getting the Right Test AND Getting Paid**
  Jane Dickerson – Seattle Children's Hospital
- **Be positive: Utility of Benchmarking in Laboratory Stewardship**
  Joe Rudolph – University of Minnesota
- **"Systems" Stewardship: Adventures in care group and health plan stewardship, medical coverage policy, and prior notification**
  Shellie Kieke – HealthPartners
- **Lab-Pharmacy Collaboration – Benefits of Multi-disciplinary Teamwork**
  Danielle Kauffman – ARUP
- **Case Studies in Laboratory Stewardship**
- **Insurance Round Table with local payers**

PLUGS On the Road(ish)

AACC — Better health through laboratory medicine.

Anaheim, California
August 4-8th

GENETIC HEALTH INFORMATION NETWORK SUMMIT

Nashville, TN
September 9-11th

WIGCA — Marshfield Clinic Health System

Wisconsin Genetics Exchange
Marshfield, Wisconsin
September 20th

Los Angeles PLUGS member meet-up!

August 19th

The PLUGS team will be in LA and is looking forward to meeting with members to discuss stewardship wins, challenges and ideas. Contact PLUGS@seattlechildrens.org if you would like to participate.

ASCP2019

Phoenix, Arizona
September 11-13th

AMA

CPT Editorial Panel Meeting
Seattle, Washington
September 26-28th

Global Genes® Allies in Rare Disease

San Diego, California
September 18-20th
Booth #108

CHILDREN'S HOSPITAL ASSOCIATION

San Antonio, Texas
September 25-26th

Choosing Wisely Implementation Committee

Join the new PLUGS committee!

The committee will be focused on implementation of Choosing Wisely with a focus on non-genetic testing.

The goal of the committee will be to share tips on changing ordering behavior around the recommendations and sharing times when the recommendations may not apply to all populations so that appropriate exceptions can be made.

Email *PLUGS@Seattlechildrens.org* if you're interested in participating!

Next PLUGS Member Meeting

September 19th, 2019, 11am (PT)