Development of In-house PGx Testing at Children's Mercy

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Children's Mercy Kansas City

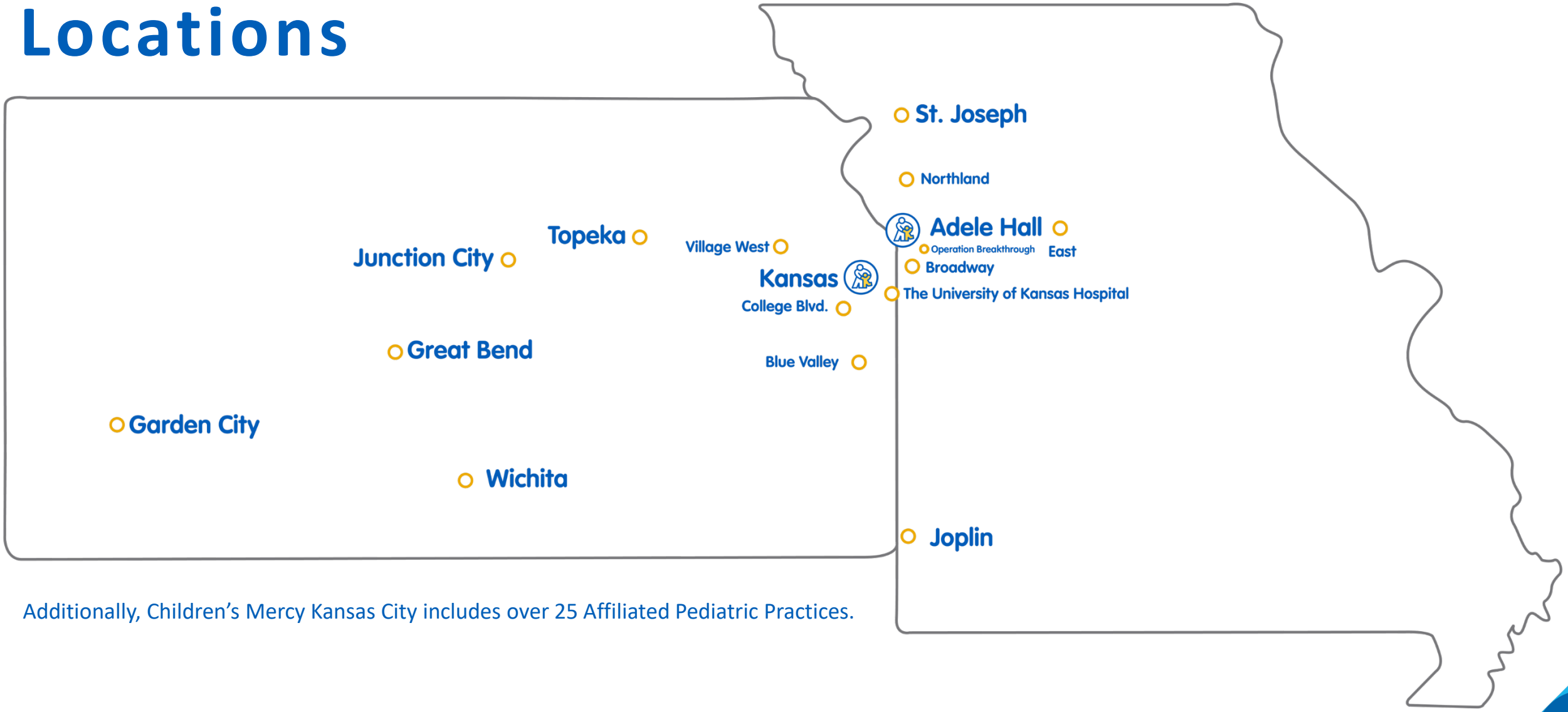
- Non-profit independent children's hospital
- Founded in 1897
- 8,000+ employees
- 800+ faculty members
- 3,000+ nurses
- 1,000+ allied health professionals
- More than 700 volunteers

Children's Mercy KANSAS CITY Research Institute

The Region's Pediatric Health System of Choice

- 390 beds
- 335,734 outpatient visits
- 202,496 ER/UC visits
- 14,345 admissions
- 19,469 surgeries
- 5,942 transports

Locations

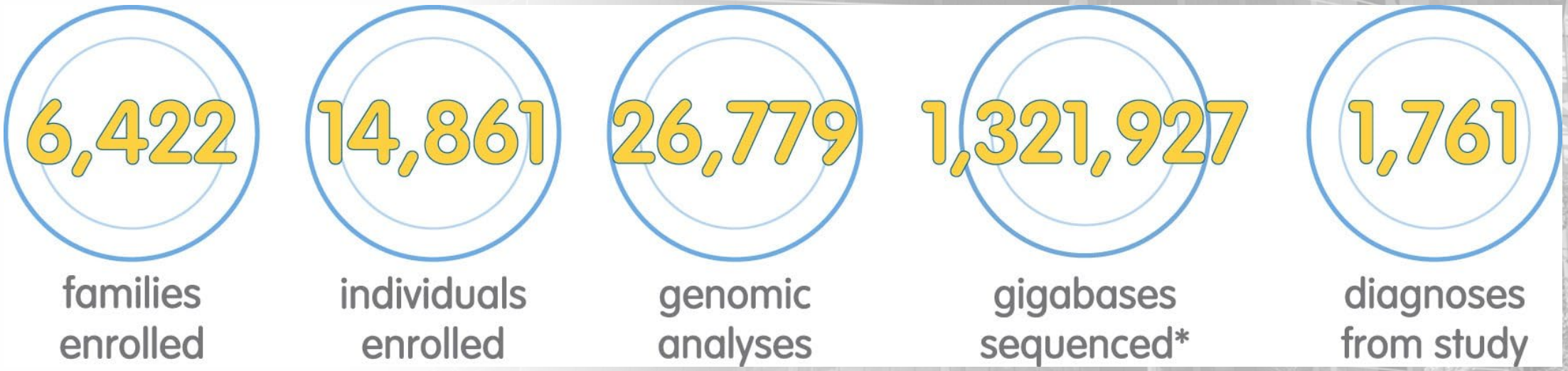


Additionally, Children's Mercy Kansas City includes over 25 Affiliated Pediatric Practices.

Children's Mercy KANSAS CITY | Research Institute

Leaders in Clinical Genomics

- 5-base HiFi long read sequencing used clinically for diagnosis
- Cancer patients get short read exome sequencing of germline and tumor (long read in validation)
- Genomic Answers for Kids research study



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Leaders in Pharmacogenetics

- Home of PharmVar
- Andrea Gaedigk (author on 14 CPIC guidelines)
- Steve Leeder (author on 5 CPIC guidelines)
- Laura Ramsey (author on 4 CPIC guidelines)
- GOLDILOKs clinic
- Pediatric Clinical Pharmacology Fellowship

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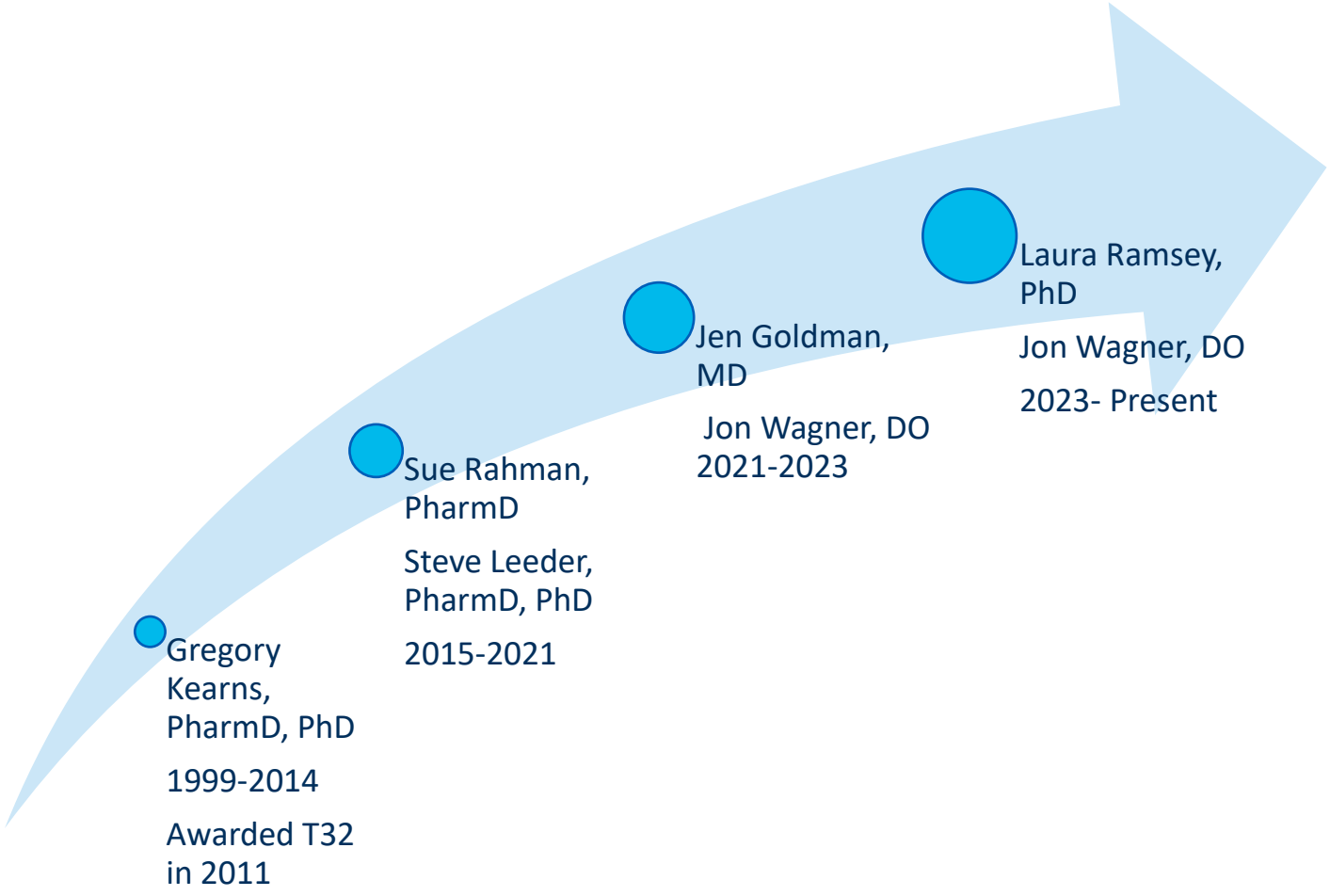
History of Clinical Pharmacology Fellowship Training at CMH

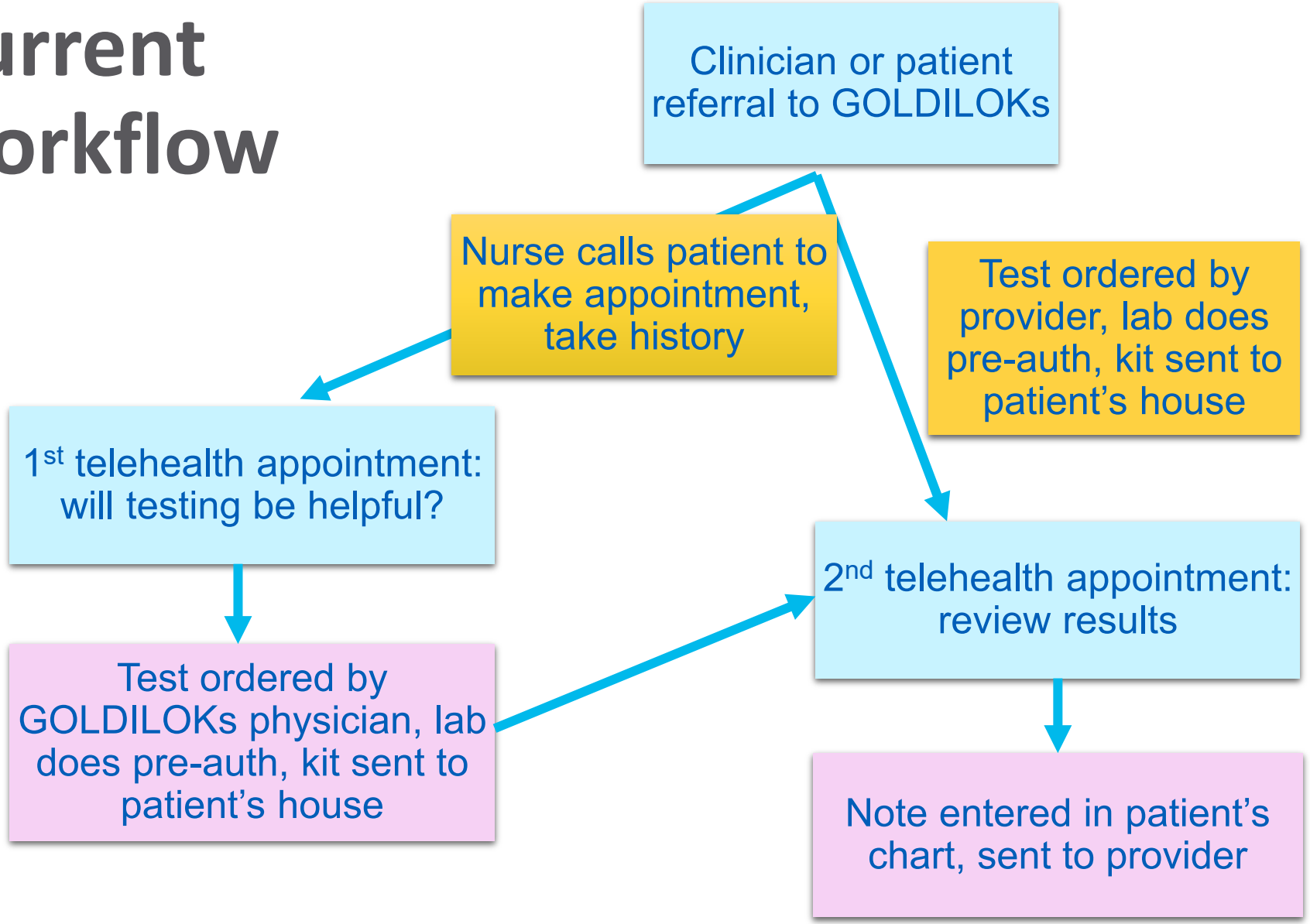


- Fellowship training started in 1999
- Total of 24 fellows trained since 1999
- 17 MD/DO, 4 PharmD/PhD, 3 PharmD, 1 APRN
- Total of 18 fellows trained since CMH awarded NICHD T32 grant in 2011
- 11 Subspecialities trained

GOLDILOKs Clinic

- Genomic and Ontogeny-Linked Dose Individualization and cLinical Optimization for KidS Clinic
- Pediatrician & pharmacist have telehealth visit with patients/families
- Nurse, social worker, PGx experts involved
- External testing labs

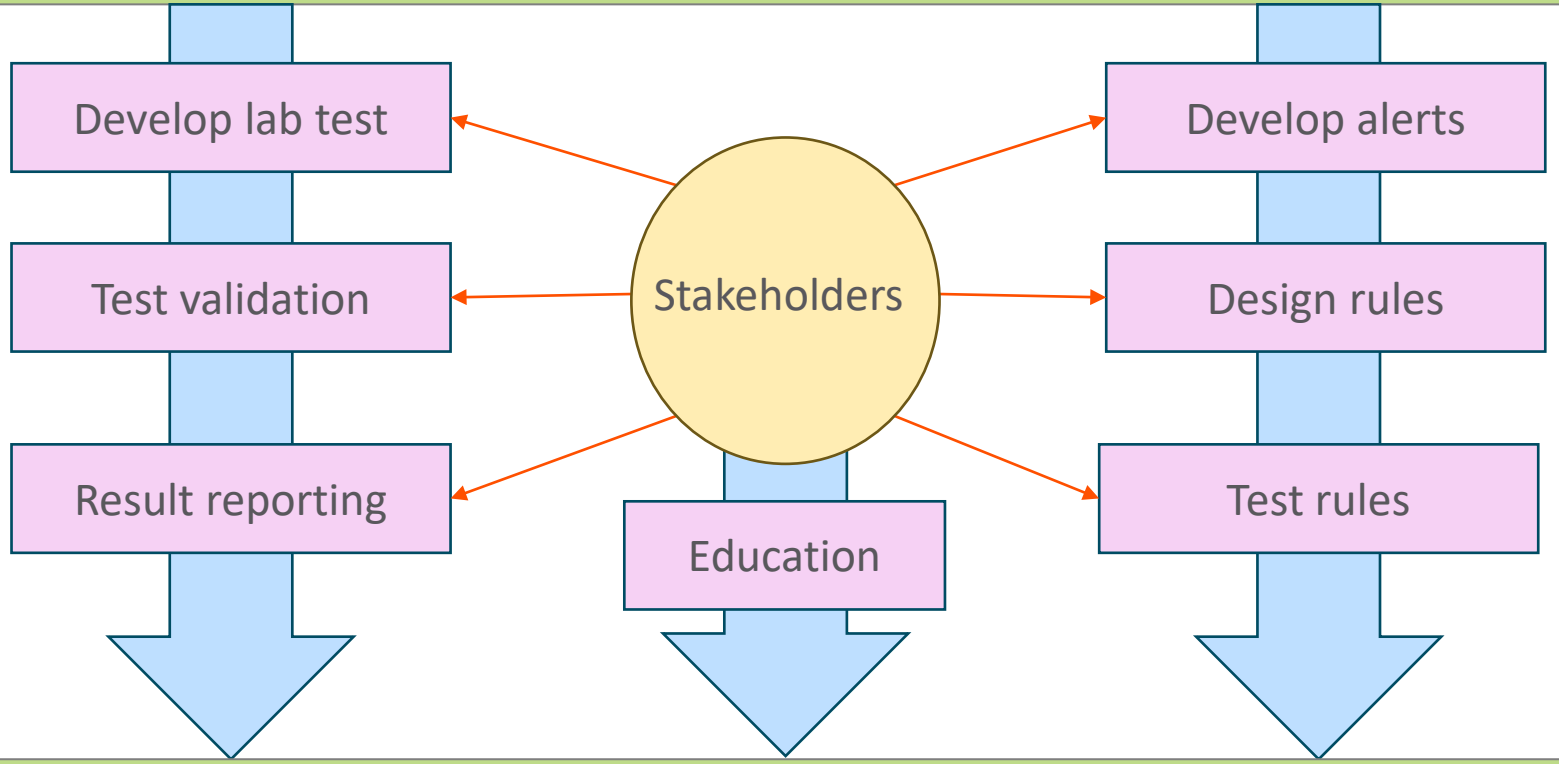
Current workflow



Opportunity to build in-house PGx testing and clinical decision support

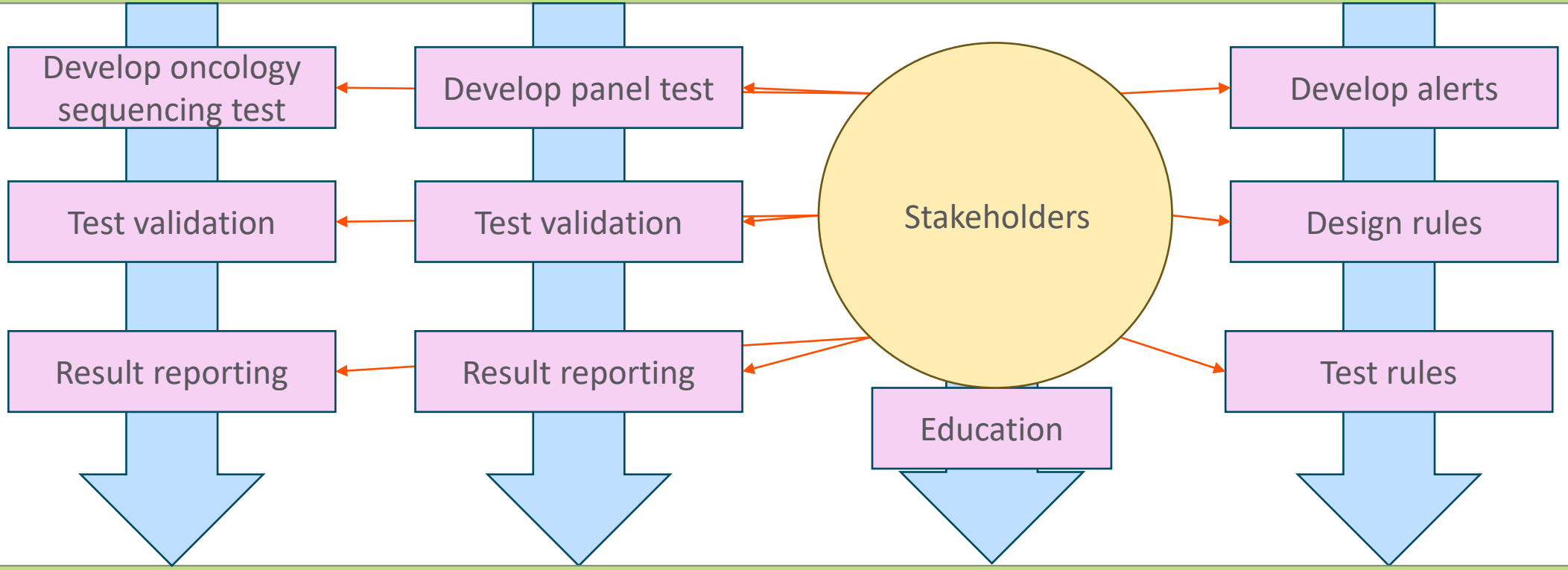
- Clinical genomics expertise
- Pharmacogenetics expertise
- Clinician buy-in
- Informatics team buy-in
- Service model
- Commercial lab stopped accepting samples from us

PGx Implementation Current State



PGx Implementation Future State

PGx Implementation Current State

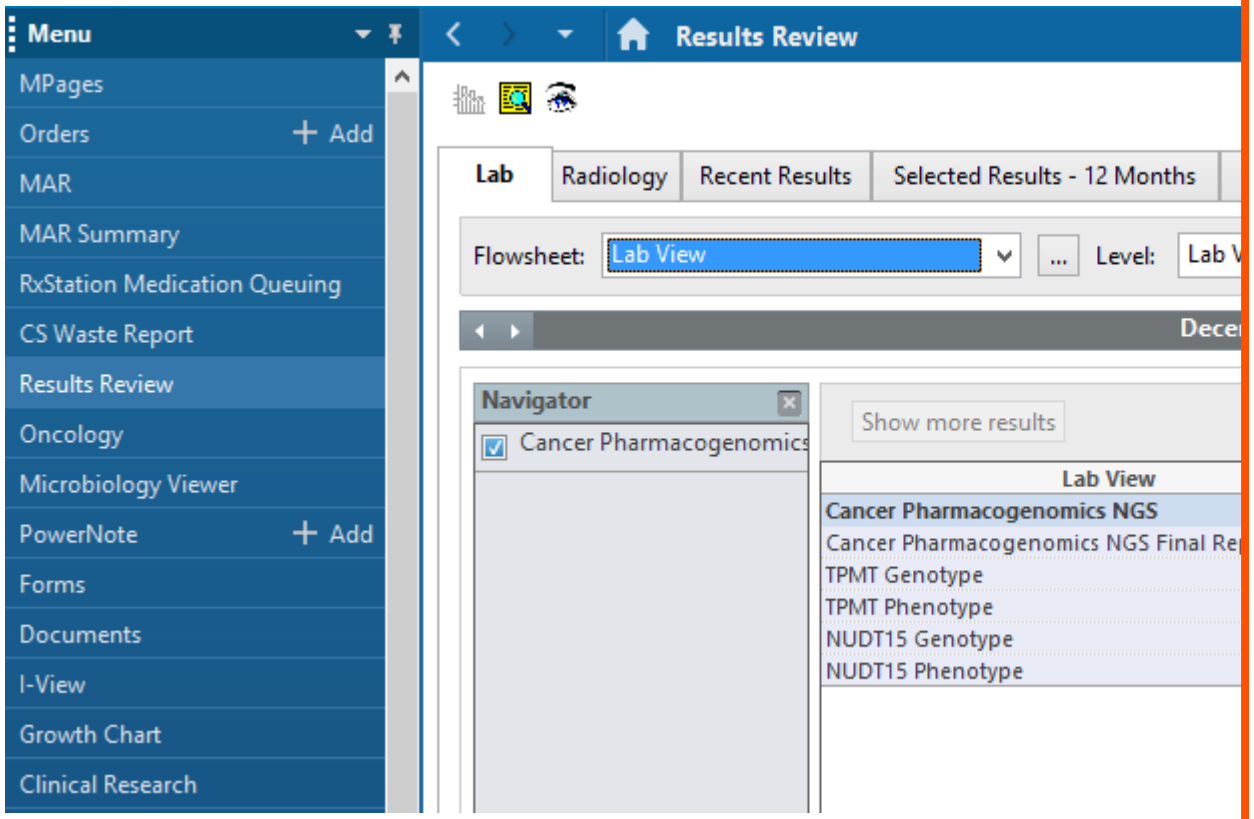


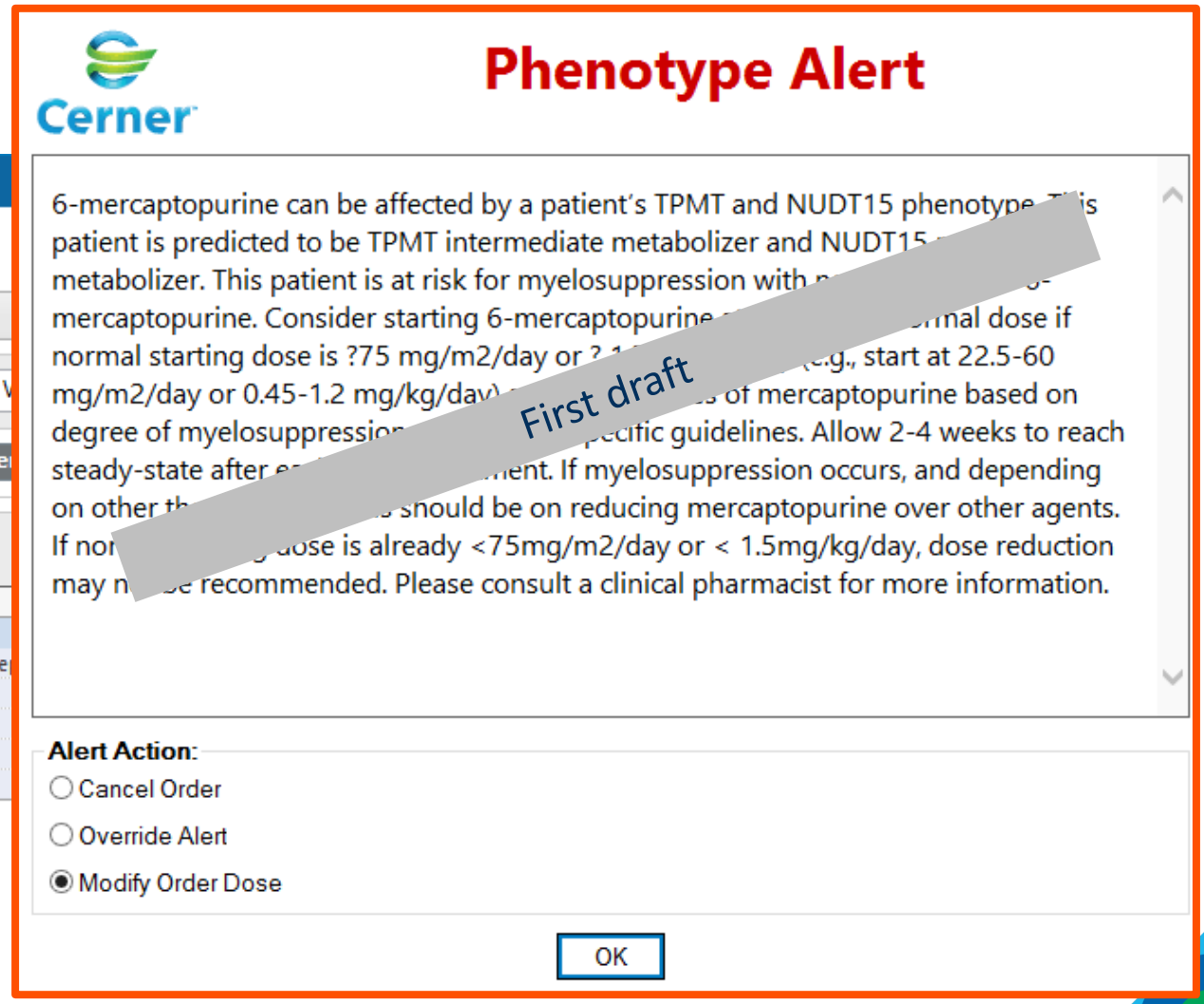
PGx Implementation Future State

Oncology PGx

- *TPMT* testing performed for leukemia patients by external lab
- *NUDT15* testing performed occasionally
- Director of Molecular Oncology & Asst Lab Director wanted to collaborate to offer *TPMT* & *NUDT15* testing from 300x short read whole exome sequencing (WES)
- Used Illumina DRAGEN™ Star Allele Caller on 10 Coriell cell line samples covering 7 *NUDT15* alleles and 6 *TPMT* alleles, 100% concordant with GeT-RM calls

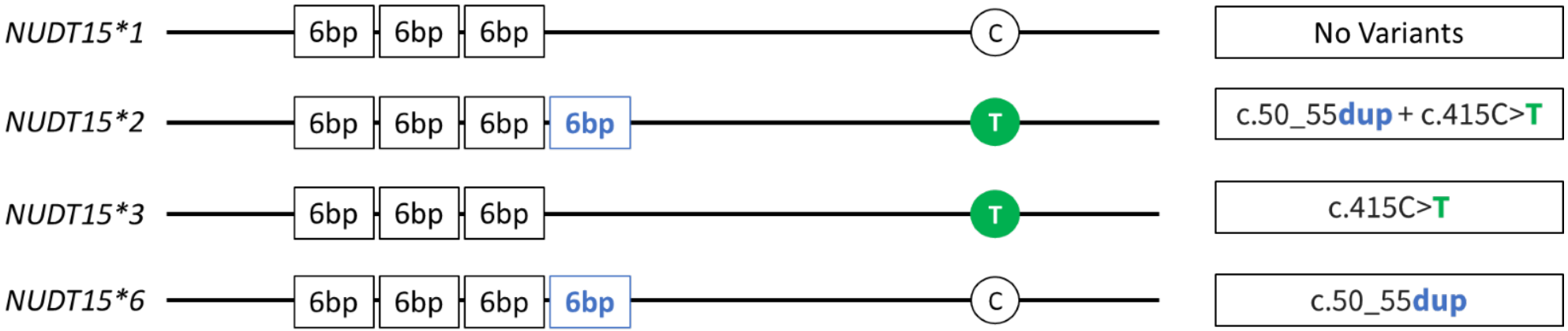
Oncology PGx CDS





Oncology PGx challenges

- Rare variants not called
  - Among 113 patients with WES, found 2 exonic *TPMT* variants, p.E98* (rs72552739) and p.Thr113= (rs17839843)
- Phasing with short reads not possible
  - The *NUDT15* result cannot be fully distinguished between **1/*2* (IM) and **3/*6* (PM). Genotyping the patient's biological parents could aid in assessing the true metabolizer status.



Oncology PGx challenges cont.

- Coverage of some pharmacogenes on WES is poor
  - Upcoming switch to long read sequencing

- Clinical Decision Support
  - Ordering of mercaptopurine place holder
  - First gene-drug pair to be implemented so lots of learning

- Ordering add-on test
  - Genetics lab intercepts orders for send out *TPMT* testing and encourages replacement with sequencing test for both genes

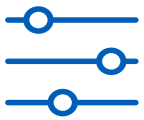
- Turn around time ~45 days

KidDose panel test

- Performed on QuantStudio™ 12K Flex instrument with 384-well format
- Custom-designed TaqMan™ panel including modifications to existing PGxExpress content:
  - Added *CYP2D6*, *CYP2C9*, *TPMT*, *NUDT15*, *SLCO1B1* variants and *CYP2D6* copy number (5'UTR, Exon 9)
  - Removed *CYP1A2*, *ABCB1*, *ADRA2A*, *F2*, *F5*, *MTHFR*
- Panel approach and workflow is designed to cover AMP Tier 1 & 2 alleles, be low-cost and competitive with external offerings, and a TAT of 10 days or less
- Validation process is underway

Panel test challenges

- There are no TaqMan® assays for some variants of interest (*CYP2D6*21, CYP3A4*20*)



- Most common haplotype assumed – not able to be phased

- You can’t see what you don’t test for

- Lack of support in training on instrument & software

PGx from long read whole genome sequencing

Advantages

- Phasing of haplotypes
  - no more *NUDT15*1/*2* or **3/*6*
- Calling alleles with variants in non-coding regions
  - *CYP2C19, CYP3A5*
- Accurate *CYP2D6* hybrid allele calls
- Others have done it
- Discovery of novel alleles

Disadvantages

- New analysis pipeline to develop and validate
- What to do with novel alleles?
- Longer turn around time for results than panel test
- Lots of data

Clinical lab

JD Nolen
Carol Saunders
Midhat Farooqi
Lisa Lansdon
Joe Alaimo
Melanie Patterson
Byunggil Yoo
Jeff Johnston
Lee Zellmer

Clinical champions

Clinical Pharmacology & GOLDILOKs

Jon Wagner
Tracy Sandritter
Alexa Pagano
Sarah Suppes
Anne Eveland
Casey Weston
Erin Boone
Wendy Wang
Stephani Stancil
Andrea Gaedigk
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