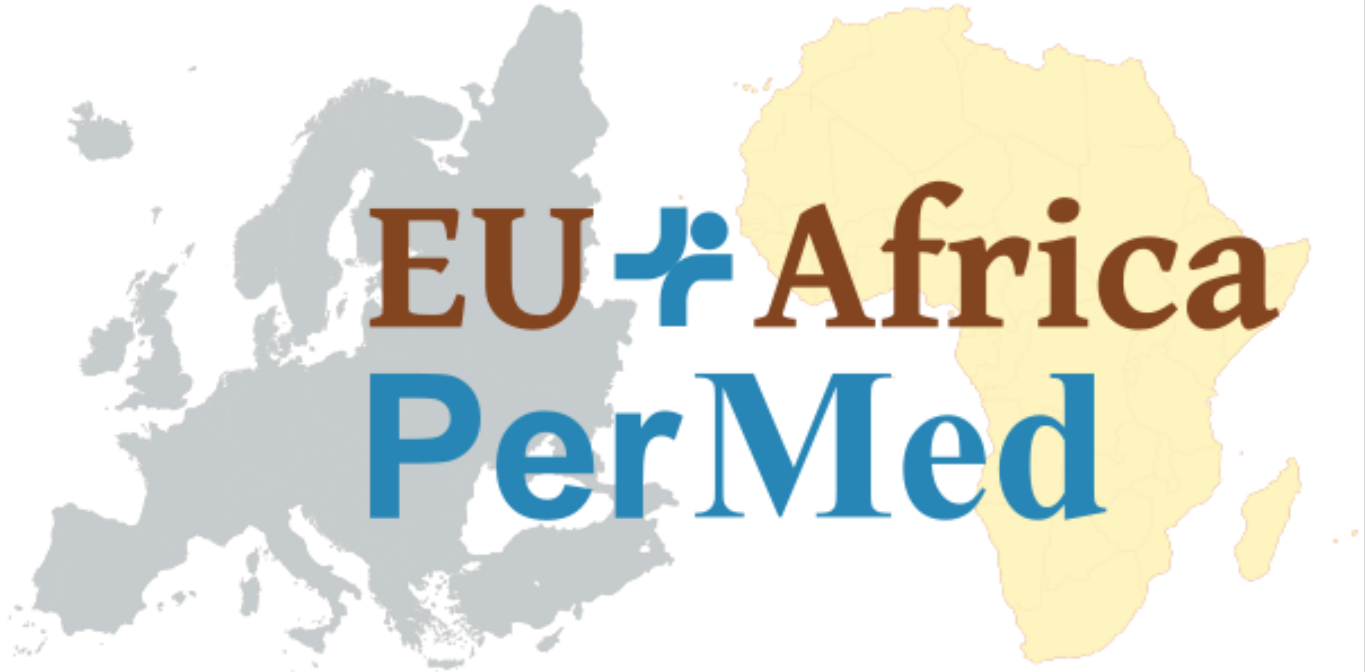
# Implementing Pharmacogenomics Testing for Effective Care and Treatment in Africa (iPROTECTA)

**A BMGF-JC Funded Initiative**

Collen Masimirembwa (Zimbabwe)

&

Julia Stingl (German)




**BUILDING LINKS BETWEEN EUROPE AND AFRICA IN PERSONALISED MEDICINE**

EU-Africa PerMed has received funding from the European Union's Horizon 2020 Research and Innovation programme under grant agreement No 964333

# Recent activities: 2017- now

- Training of PhD students in PGx – GHPP
- Training of MSc in Genomics & Precision Medicine – EDCTP
- PGx of rosuvastatin - AstraZeneca
- PGx of Tamoxifen – Novartis
- PGx of TB DILI – GSK/Novartis/SAMRC
- PGx of HT – SAMRC
- iPROTECTA – BMGF-JC

EU+Africa PerMed

# Where we are….

*Global Health, Epidemiology and Genomics*

**cambridge.org/ghg**

2018

## An upward trajectory of genomic publications from Africa: cautious optimism for a turning tide

Michèle Ramsay

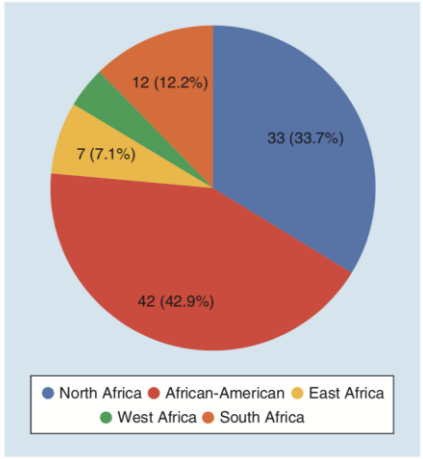
| | Genomics | | | GWAS | | | Pharmacogenomics | | |
|---|---|---|---|---|---|---|---|---|---|
| Publication date | Total | Africa | % Africa | Total | Africa | % Africa | Total | Africa | % Africa |
| 1998–2002 | 8279 | 29 | 0.35 | 86 | 1 | 1.16 | 1837 | 15 | 0.82 |
| 2003–2007 | 28 432 | 166 | 0.58 | 643 | 8 | 1.24 | 4417 | 26 | 0.59 |
| 2008–2012 | 48 979 | 359 | 0.73 | 12 189 | 109 | 0.89 | 5881 | 56 | 0.95 |
| 2013–2017 | 90 421 | 1682 | 1.86 | 18 883 | 314 | 1.66 | 8123 | 160 | 1.97 |
| Total | 176 111 | 2236 | 1.27 | 31 801 | 432 | 1.36 | 20 258 | 257 | 1.27 |

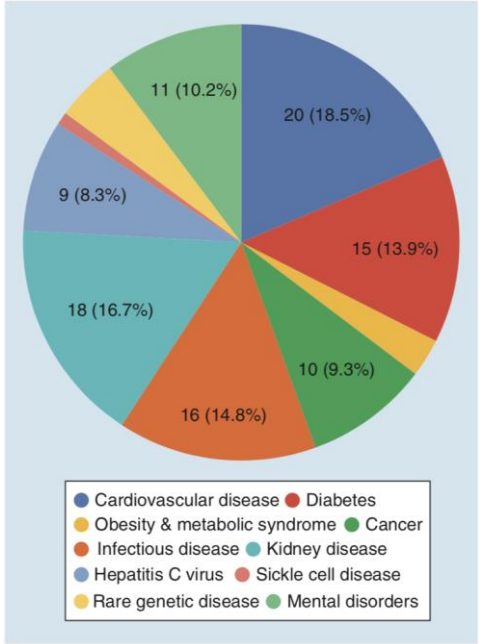
1.27% of Global PGx publications

*Per Med.* 2020 March ; 17(2): 155–170. doi:10.2217/pme-2019-0110.

## A review of clinical pharmacogenetics Studies in African populations

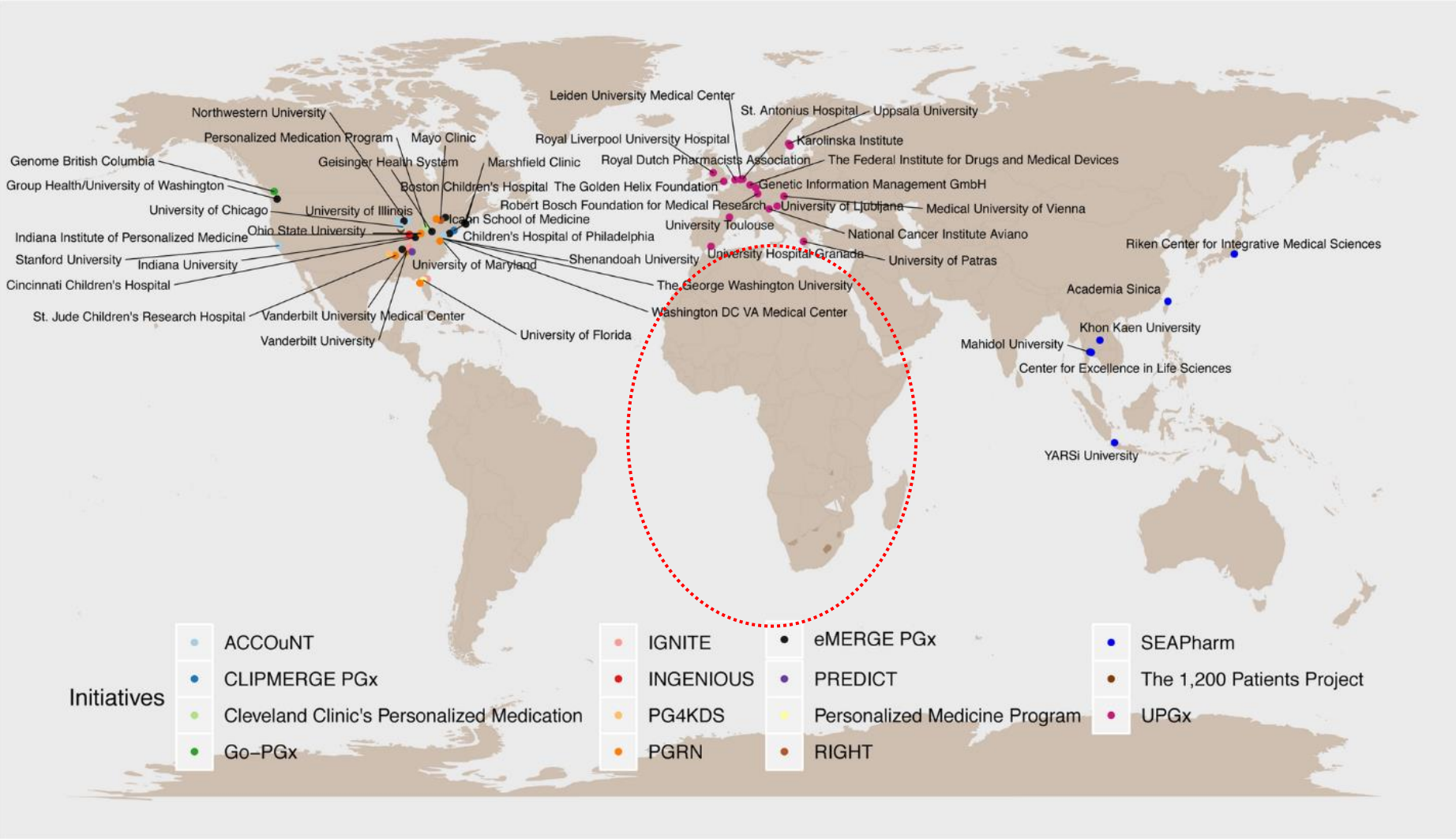
**Fouzia Radouani[1], Lyndon Zass[2], Yosr Hamdi[3], Jorge da Rocha[4], Reem Sallam[5], Sonia Abdelhak[3], Samah Ahmed[6,7], Maryame Azzouzi[1], Ichrak Benamri[1,8], Alia Benkahla[9],**




<1% of Global Clin PGx studies

# Clinical Implementation PGx Programs




Krebs and Milani, 2019

# What we are doing about it……

- ❑**Building infrastructure for genomics and bioinformatics**
- ❑**Strengthening the skilled manpower base**
- ❑**Conducting translational precision medicine research**
- ❑**Building international collaborations**

# Training: MSc Genomics and Precision Medicine

**9 students graduated: Benin – 1, Nigeria – 2, Kenya – 3, and Zimbabwe - 3**

# 2022 Pilot studies to identify important DGIs

Received: 22 September 2022 | Revised: 15 December 2022 | Accepted: 28 December 2022
DOI: 10.1111/bcp.15659

SHORT COMMUNICATION

## Cardiotoxicity and pharmacogenetics of doxorubicin in black Zimbabwean breast cancer patients

Vincent Aketch Nyangwara[1,2] | Tinashe Mazhindu[1,4] | Zedias Chikwambi[1,2] | Collen Masimirembwa[1] | Thomas B. Campbell[3] | Margaret Borok[4] | Ntokozo Ndlovu[5]

Journal of Personalized Medicine

*Communication*

## Pharmacogenetics and Adverse Events in the use of Fluoropyrimidine in a cohort of cancer patients on standard of care treatment in Zimbabwe

Boluwatife Lawrence Afolabi[1,2], Tinashe Mazhindu[1,3], Chikwambi Zedias[1,2] Margaret Borok[3], Ntokozo Ndlovu[3], Collen Masimirembwa[1], and Consortium for Genomics and Therapeutics in Africa (CGTA)

Journal of Personalized Medicine
MDPI

*Article*

## Pharmacokinetics of Tamoxifen and Its Major Metabolites and the Effect of the African Ancestry Specific CYP2D6*17 Variant on the Formation of the Active Metabolite, Endoxifen

Comfort Ropafadzo Kanji [1,2,*], Georginah Nyabadza [1], Charles Nhachi [2] and Collen Masimirembwa [1,3,*]

## Effects of genetic polymorphisms of drug metabolizing enzymes and co-medications on tamoxifen metabolism in black South African women with breast cancer

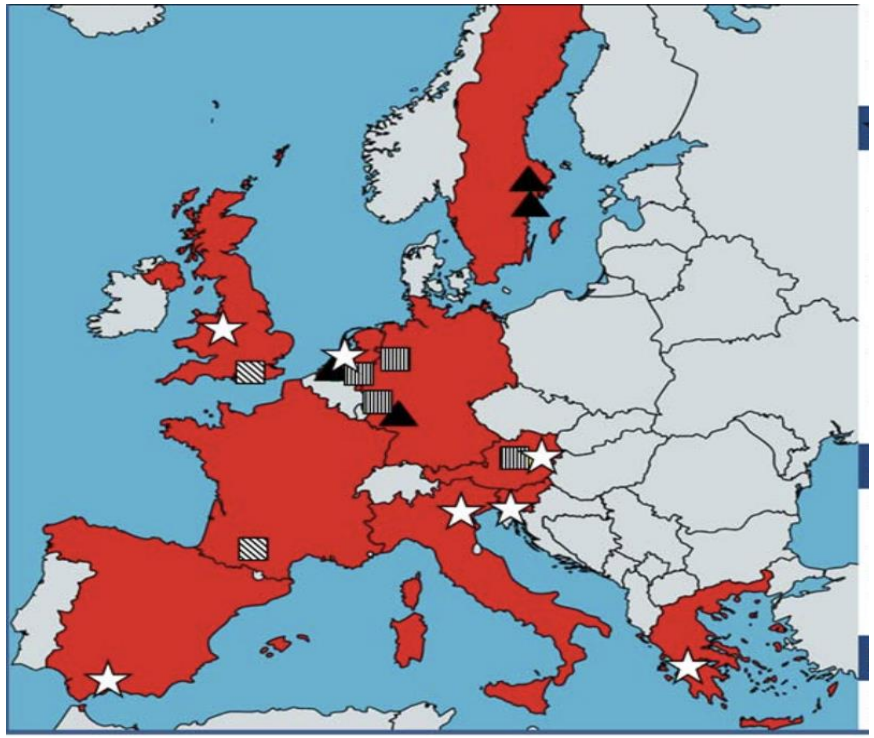
Shingirai M. Chiwambutsa[1,2] (Msc), Oluwatosin Ayeni[3,4] (MBChB, PhD), Nyasha Kapungu[13] (Msc), Comfort Kanji[13] (Msc), Roslyn Thelingwani[13] (PhD), Wenlong Carl Chen[1,3,14] (PhD), Dikeledi H. Mokone[11] (MBChB, MMed), Daniel S O'Neil[12] (MD, MPH), Alfred I. Neugut[5,9,10] (MD, PhD), Judith S. Jacobson[9,10] (DrPH, MBA), Paul Ruff[3,4,7] (MBChB, MMed), Herbert Cubasch[3,6,7] (MBChB), Maureen Joffe[3,7,8] (PhD), Collen Masimirembwa[1,13] (PhD)

# Some emerging facts from pilot studies

- Pediatric PGx guidelines in the sue of doxorubicin not applicable to adult breast cancer patients
- DPYD variants in current PGx guidelines in the use of 5-FU are absent in the Zimbabwean population leaving observed ADRs unexplained
- The African Specific CYP2D6*17 and *29 have clinically significant effects on Tamoxifen use. Based on the Activity score of 0.30 we determined, patients carrying these variants could benefit from dose increase
- Analysis of pilot study results for drug-gene interactions involving warfarin-CYP2C9, clopidogrel-CYP2C19, isoniazid-NAT-2, CYP2D6-opiods, and TMTP-thiopurines are in progress.

# Inspired by the IGNITE (USA) and the PREPARE (Europe) implementation programs

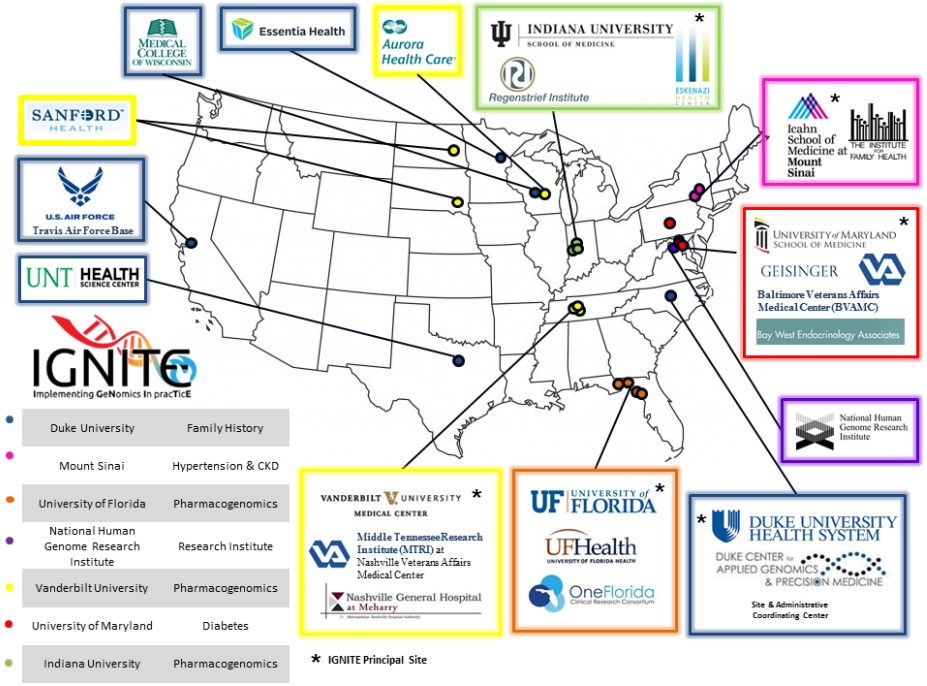
EU funded



- **Countries:** Ita, UK, Aus, Gre, Spa, Net, Slo
- **Study period:** 2015
- **Design:** Randomized Case-Control
- **Sample size:** 8 000 patients
- **PGx Test:** 13 genes, 48 variants
  39 drug-gene pairs

van der Wouden et al., 2017

NIH funded




- 5 research sites ( 3 on PGx)
- Start in 2013
- Implementation
- 100 to 10 000 per study
- Few to many drug-gene pairs

https://gmkb.org/ignite-gdp/

# Encouraging Results from UPGx-PREPARE Study

## A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

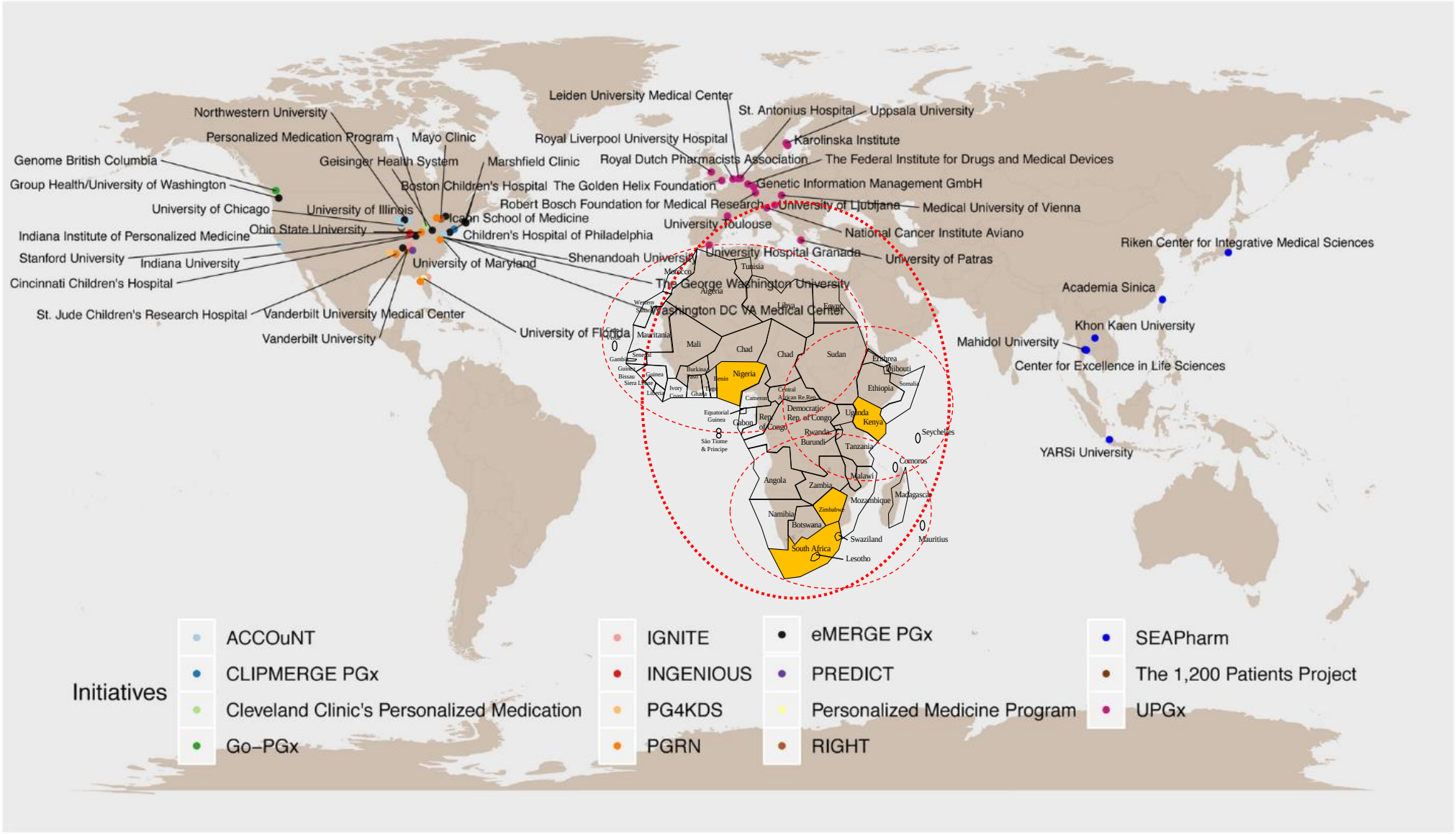
*Lancet* 2023; 401: 347–56

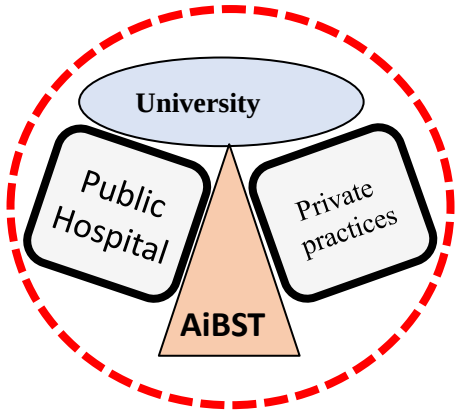
*Jesse J Swen, Cathelijne H van der Wouden*, Lisanne EN Manson*, Heshu Abdullah-Koolmees, Kathrin Blagec, Tanja Blagus, Stefan Böhringer, Anne Cambon-Thomsen, Erika Cecchin, Ka-Chun Cheung, Vera HM Deneer, Mathilde Dupui, Magnus Ingelman-Sundberg, Siv Jonsson, Candace Joefield-Roka, Katja S Just, Mats O Karlsson, Lidija Konta, Rudolf Koopmann, Marjolein Kriek, Thorsten Lehr, Christina Mitropoulou, Emmanuelle Rial-Sebbag, Victoria Rollinson, Rossana Roncato, Matthias Samwald, Elke Schaeffeler, Maria Skokou, Matthias Schwab, Daniela Steinberger, Julia C Stingl, Roman Tremmel, Richard M Turner, Mandy H van Rhenen, Cristina L Dávila Fajardo, Vita Dolžan, George P Patrinos, Munir Pirmohamed, Gere Sunder-Plassmann, Giuseppe Toffoli, Henk-Jan Guchelaar, on behalf of the Ubiquitous Pharmacogenomics Consortium†*

- ❑ Successful multi-center study involving 7 countries
- ❑ >90% of the 7000 patients had at least one actionable DGI
- ❑ Genetic results turn-around-time was 7 days

**PGx guided prescription reduced ADRs by 30%**

# Implementing **P**harma**c**o**g**enomics **T**esting for **E**ffective **C**are and **T**reatment in **A**frica (iPROTECTA)




**Genomics & Therapeutics Unit**

1. Nigeria
2. Kenya
3. Zimbabwe
4. South Africa

**Africa joining Global Clinical PGx programs through the *i*PROTECTA project**

# The iPROTECTA program approach

- 10-year implementation program to test the feasibility and effectiveness of PGx based precision medicine in 10 000 patients in Nigeria, Kenya, Zimbabwe and South Africa

- Gene-Drug-Disease choice to be based on:
  - Strength of existing evidence in CIPIC and DWPG Clinical PGx guidelines
  - Pilot data on the potential importance of a drug-gene interaction in Africa
  - Importance of drug-disease pairs in participating countries
  - Broad feasibility with respect to infrastructure, skilled manpower & regulatory environment

- Program includes capacity building with respect to infrastructure, research skills, knowledge among practitioners, & regulatory matters

# iPROTECTA studies initiating 2023

- ❑iPROTECTA – Oncology - PGx in the sue of 5FU and of irinotecan
- ❑iPROTECTA – SCD – PGx in pain management with opioids
- ❑iPROTECTA – CVD – PGX in the use of clopidogrel and of warfarin

# Implementation of Pharmacogenetic Testing For Effective Care and Treatment in Africa: Oncology



## A clinical implementation study of the feasibility and effectiveness of pharmacogenomics biomarker-guided treatment in gastrointestinal cancer patients

**Protocol Number: iPROTECTA 01**

Investigation: Pharmacogenomic biomarker guided therapy (DPYD-5-Fluorouracil and UGT1A1-Irinotecan)

Principal Investigator: Tinashe Adrian Mazhindu

Study Sponsor: African Institute of Biomedical Science and Technology (AiBST)

Study Sponsor Contact: Collen Masimirembwa, PhD, DPhil

Wilkins Hospital, Block C

Corner Rekayi Tangwena & Princess road, Harare

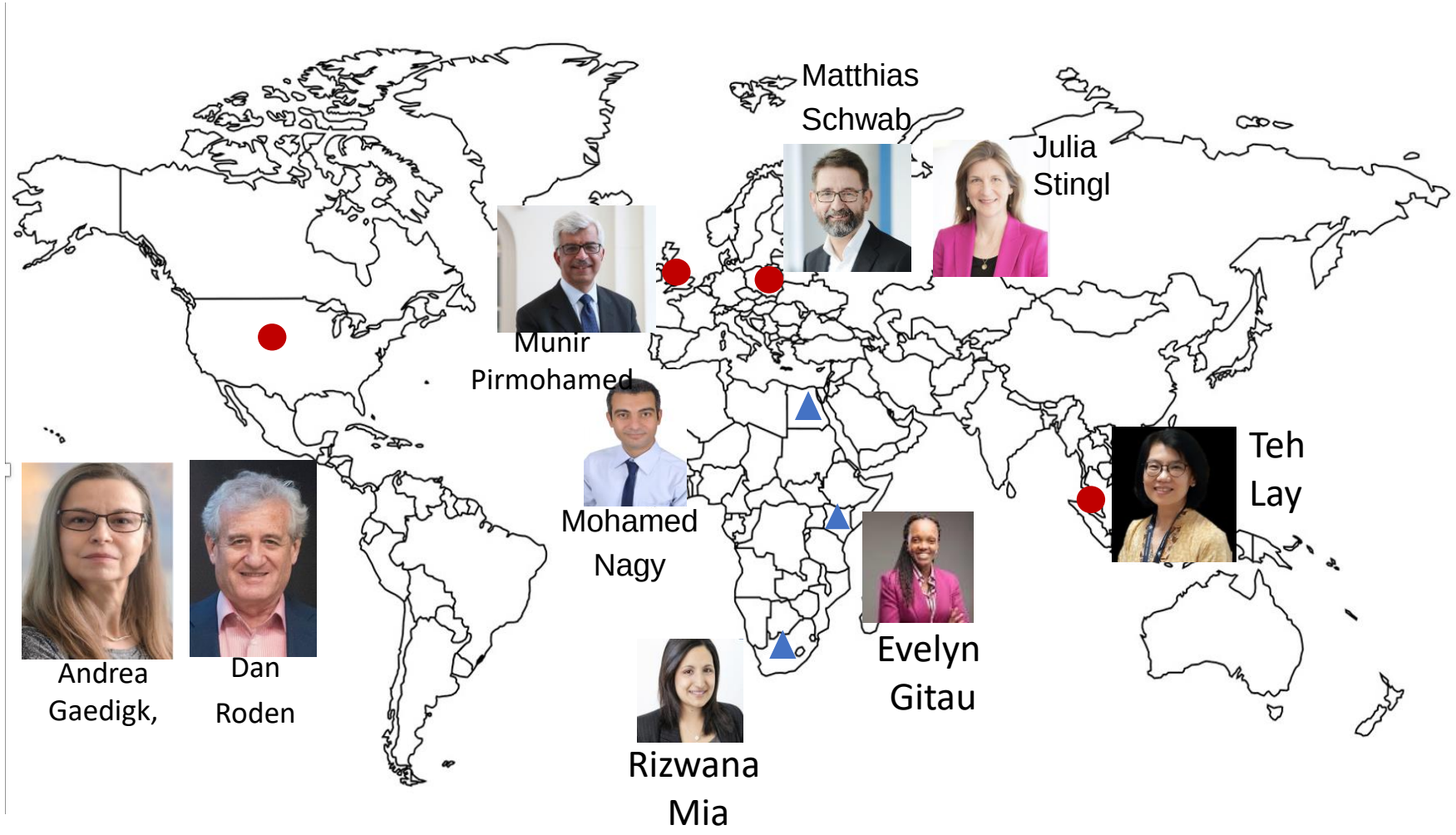


## 1. PROTOCOL SUMMARY

### 1.1 Synopsis

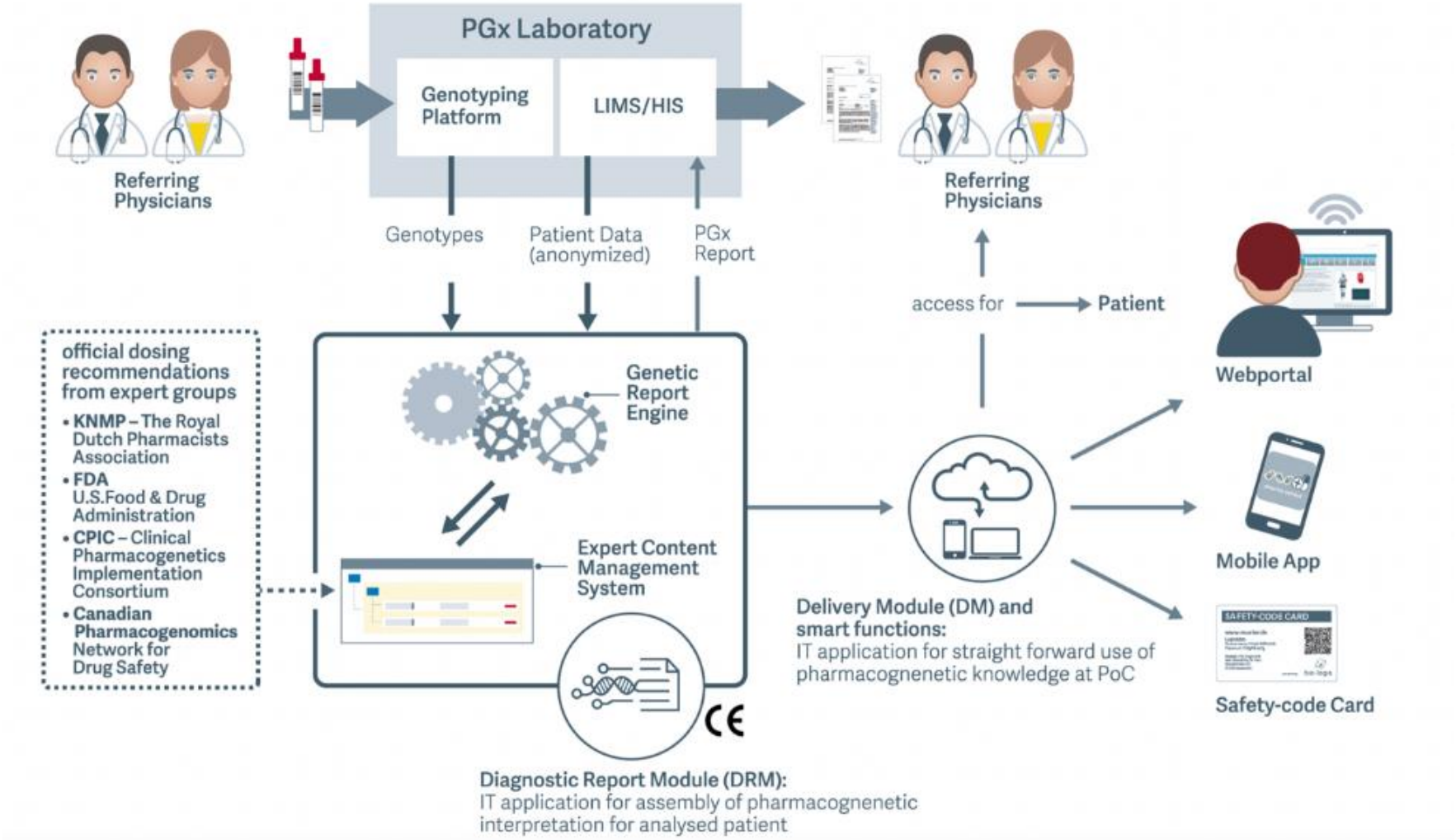
| | |
|---|---|
| Study title | A clinical implementation study of the feasibility and effectiveness of pharmacogenomic biomarker guided treatment in gastrointestinal (GI) cancer patients |
| **Study Description:** | This is an implementation study, of pharmacogenomics-guided cancer and supportive therapy interventions for GI cancer patients to evaluate feasibility and clinical effectiveness.<br>Patients with GI cancer who receive irinotecan or 5-FU (including capecitabine) based chemotherapy based on NCCN ® guidelines recommendations for cancer type and disease stage will be prescribed chemotherapy dosing guided by their pharmacogenomic biomarker based on DPWG guidelines for UGT1A1 and DPYD variants respectively with accompanying therapeutic drug monitoring.<br>**NB: There is no use of any investigational new drug in this study.** |
| **Primary Objective:** | To evaluate the implementation feasibility and effectiveness of drug selection and dose calculation based on a patient's genotype in GI cancers with respect to pharmacokinetics, drug toxicity and efficacy outcome in an African setting. |
| **Study endpoints:**<br>**Primary Endpoint** | • Dose deviation rate due to pharmacogenomics biomarker guidance and resultant drug/drug metabolite plasma concentration at estimated $T_{max}$<br>• Turnover time for pharmacogenomics results availability to clinicians to guide intervention decision making (Target time is 14 days for all patients) |
| **Secondary Endpoints** | • Numbers and proportion of patients with ≥ grade 3 toxicity (NCI CTAE v5)<br>• Turnover time for therapeutic drug monitoring results availability to clinicians to guide intervention decision making (Target time is 14 days for all patients)<br>• Disease-free and overall survival of study participants<br>• Tumour objective response rate (for neoadjuvant therapy or metastatic stage patients) using the RECIST criteria.<br>• Cost-effectiveness of implementing PGx guided therapy compared to historical outcomes<br>• Quality of life (QoL) outcomes among study participants using QoL questionnaires<br>• Number of samples bio-banked out of the total planned per patient. |
| • **Exploratory Endpoints** | • PGx polymorphism impact of cancer supportive therapy outcomes- (analgesia and emesis)<br>• Cancer care biomarker and genomic mutation assessment for GI cancer patients including mapping the mutation trends |
| **Study Population** | Adults (>18 years of age) with a gastrointestinal cancer diagnosis who are receiving |

# Scientific and Technical Advisory Committee (STAC)




**Harnessing global PGx experts to help deliver iPROTECTA**

# Partnership with biologis to implement the GIMS.pharma




https://www.biologis.com/solutions/GIMS.pharma

**1. Doctor - Patient Interface**
**at different doctors & target cancer treatment sites/days**

- Consenting patient on study medicines
- Decision to refer sample for PGx testing

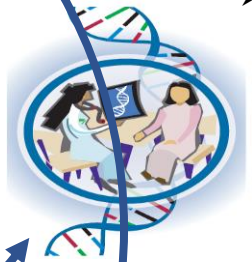
**2. Lab. Genetic test**

- Genetic variants Affecting safety & efficacy of selected cancer drugs

Report generated Based on CPIC, DPWG, CPNDS Guidelines


**3. Doctor-Patient**

- **Share results**
- **Dr implements guidelines (drug & dose selection)**



GIMS delivers results to Dr. mobile phone & hosp. EHRS

**4. Experts Clinic Day**

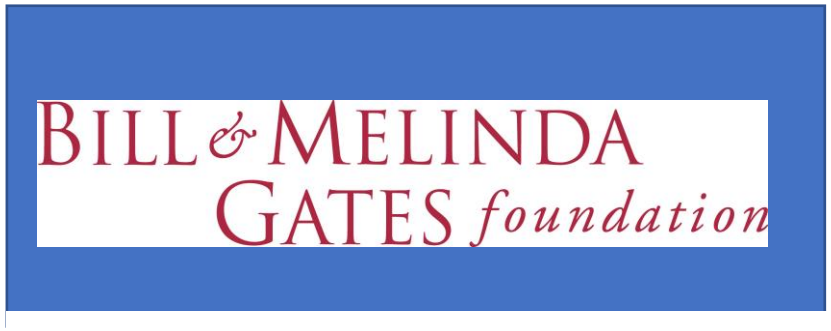
- PI presents summary data
- Drs present unique patient cases
- Experts discuss trends

# Concluding Remarks

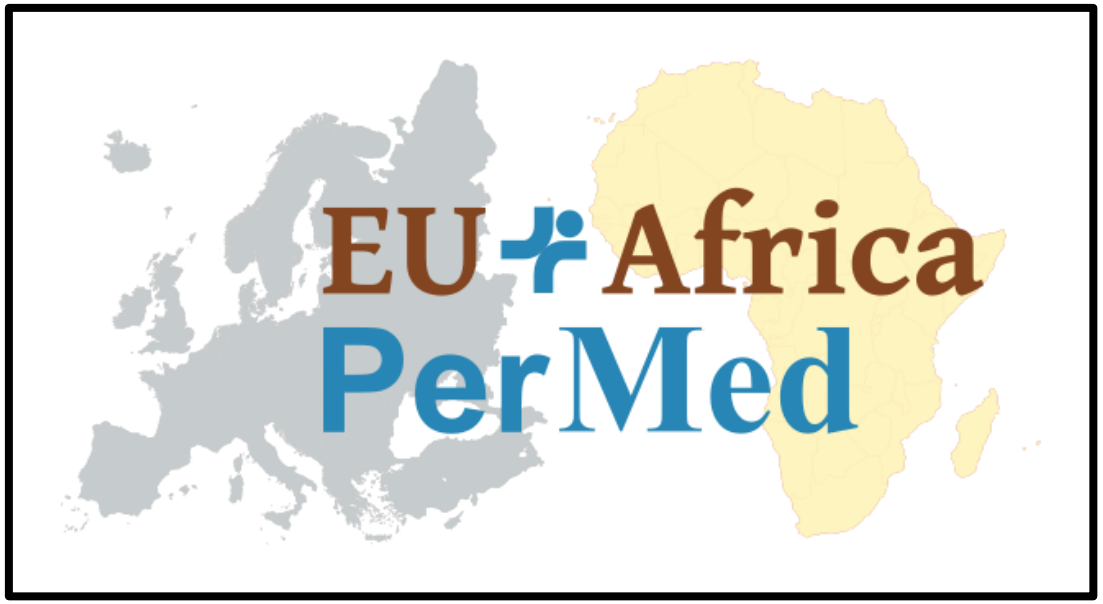
- ❑ AiBST needs to strengthen its collaborative network to achieve the iPROTECTA objectives
- ❑ Collaboration with EU-Africa PerMed could be mutually beneficial in PGx based personalized medicine
- ❑ Collaboration with industry will expediate inclusion of African populations in drug discovery & development

EU Africa PerMed

# Acknowledgements






bio·logis
digital health








# Thank You