Discovery and Validation of a Genetic Biomarker for a Triple Reuptake Inhibitor (Liafensine) in TRD

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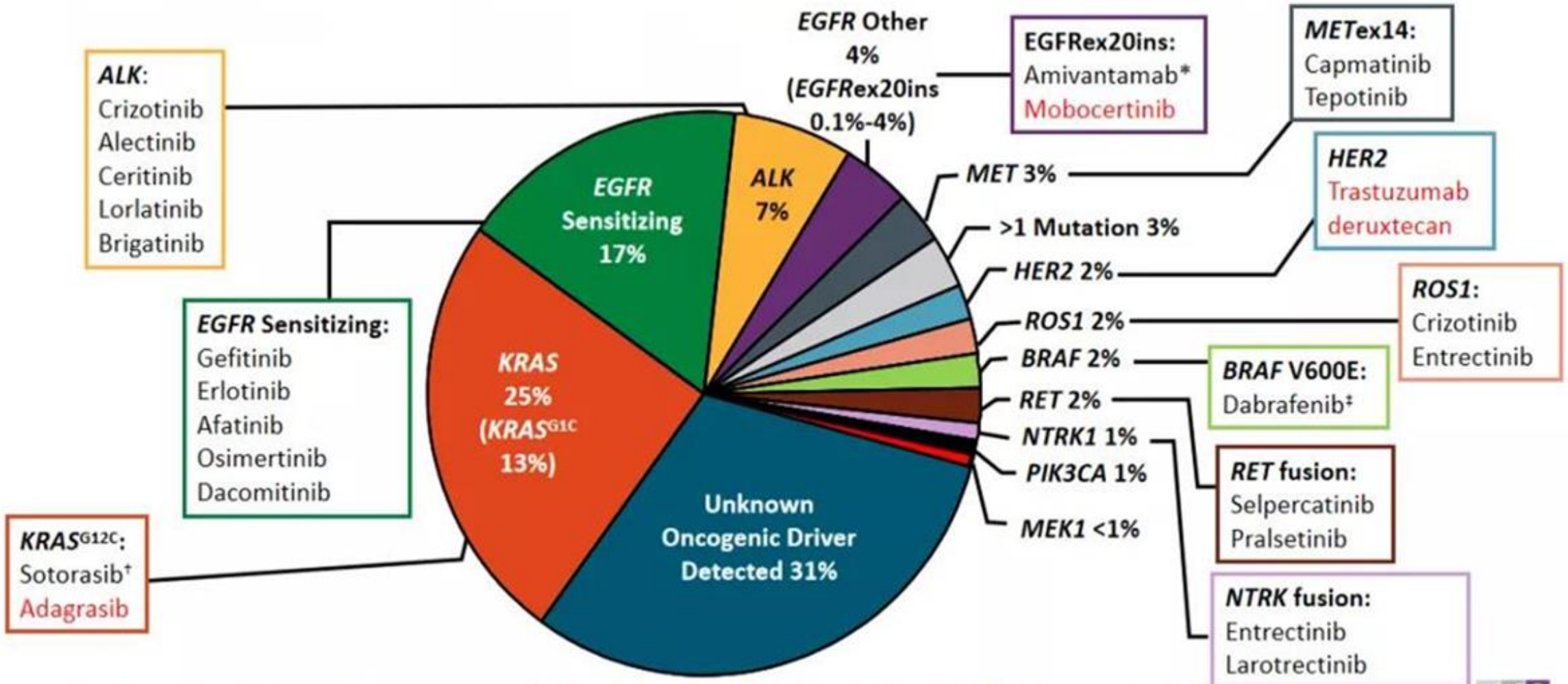
Disclosures:

The Presenter is an employee of Denovo Biopharma

Biomarkers are the Key to Many New Drug Approvals in Oncology

Lung Cancer is Treated Differently based on the Biomarkers

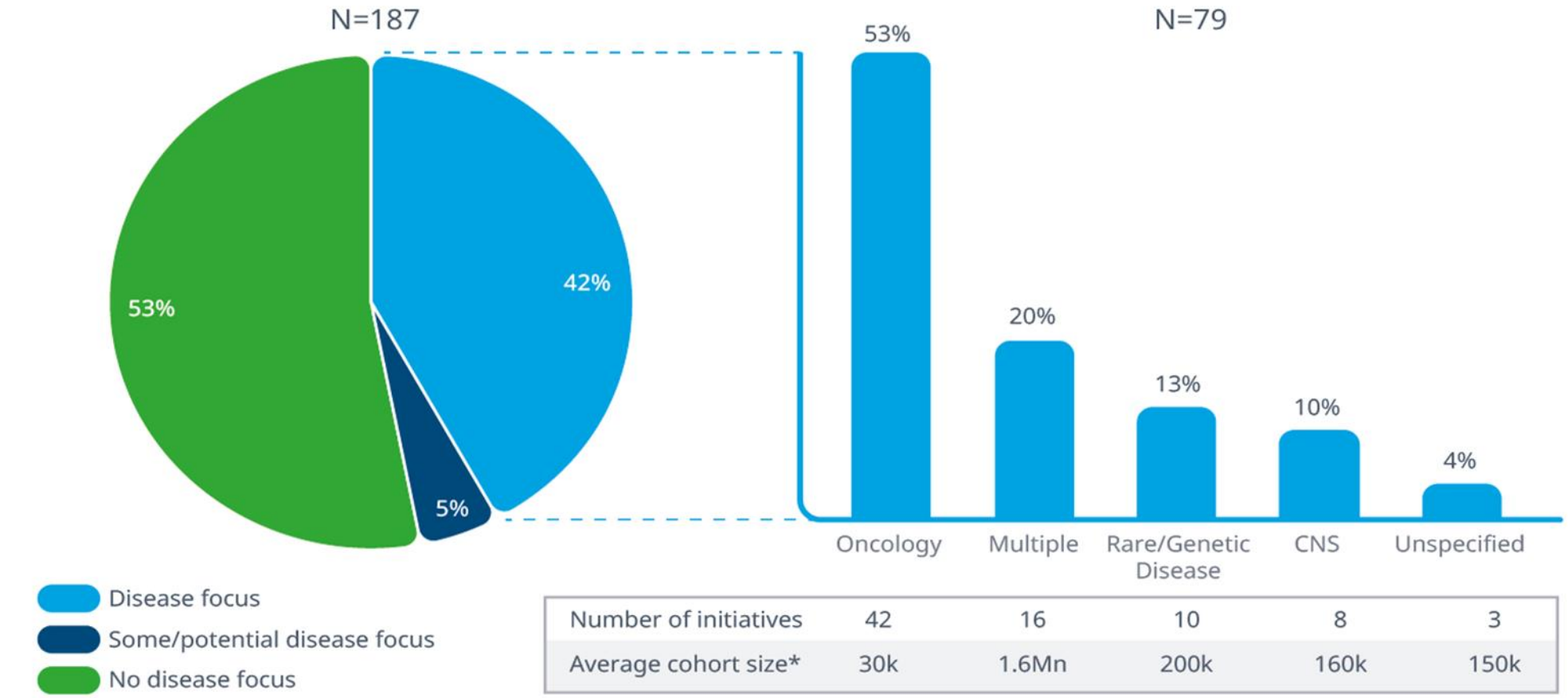


Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613. Burnett. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.

*Approved after PD on platinum-based CT. †Approved after ≥1 prior systemic therapy. ‡Approved in combination with trametinib (MEK inhibitor) for *BRAF* V600E mutation. Slide credit: clinicaloptions.com

Use of Biomarkers in CNS Diseases is Far Less Than in Oncology

Number of Genomics Initiatives by Disease Area Focus

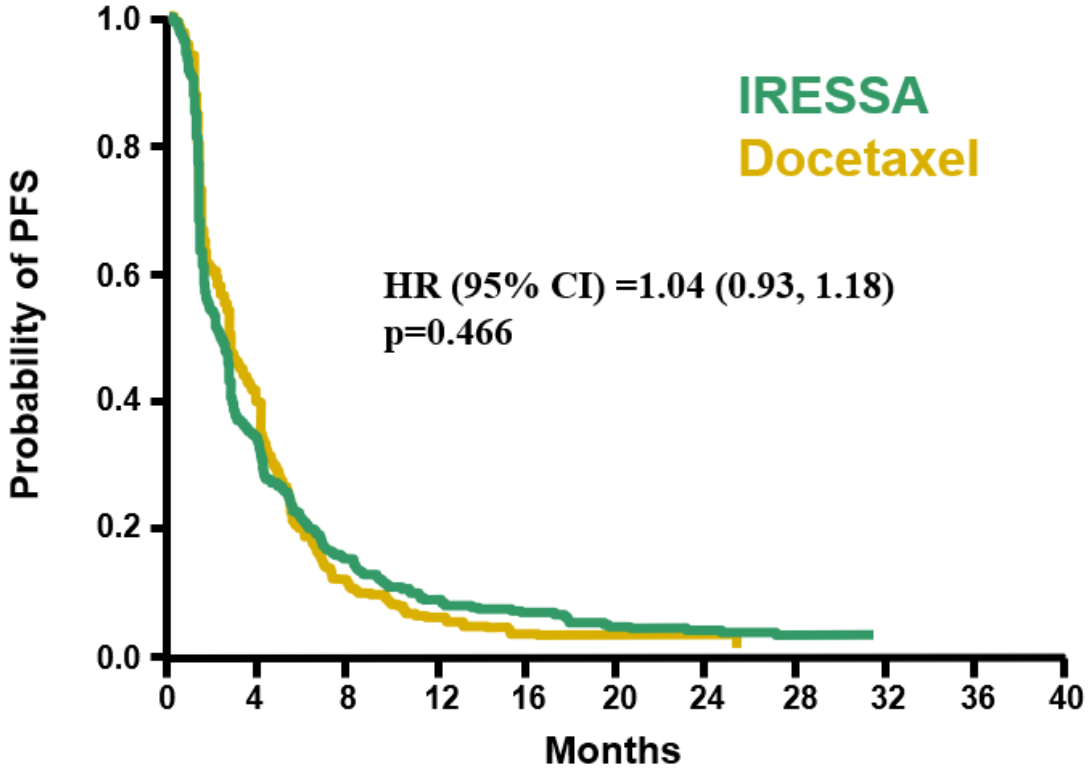


	Oncology	Multiple	Rare/Genetic Disease	CNS	Unspecified
Number of initiatives	42	16	10	8	3
Average cohort size*	30k	1.6Mn	200k	160k	150k

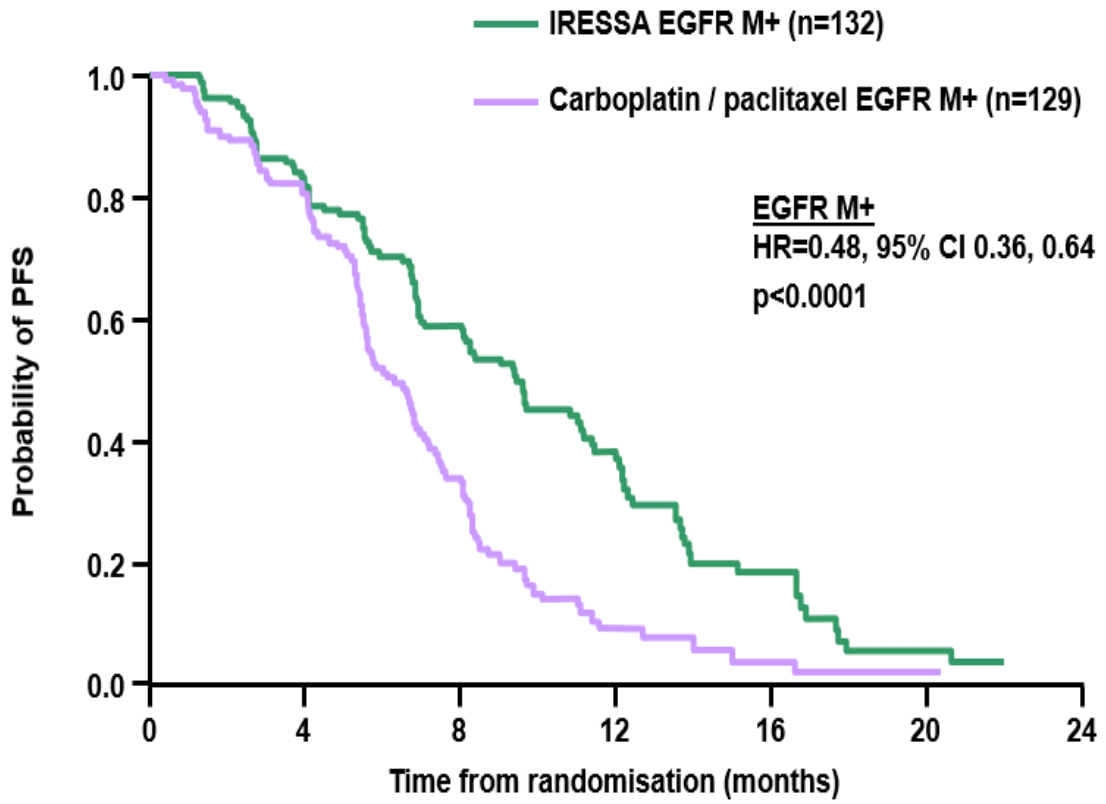
Source: IQVIA Genomic Initiatives Database, Feb 2020
Notes: Average cohort size based on target size first, current size if target unavailable, rounded to nearest 10,000.
Report: Understanding the Global Landscape of Genomics Initiatives : Progress and Promise, April 2020

The Journey of Iressa: An EGFR inhibitor for Lung Cancer

Iressa Failed in General Population



Iressa Worked Well in EGFR Mutated Patients

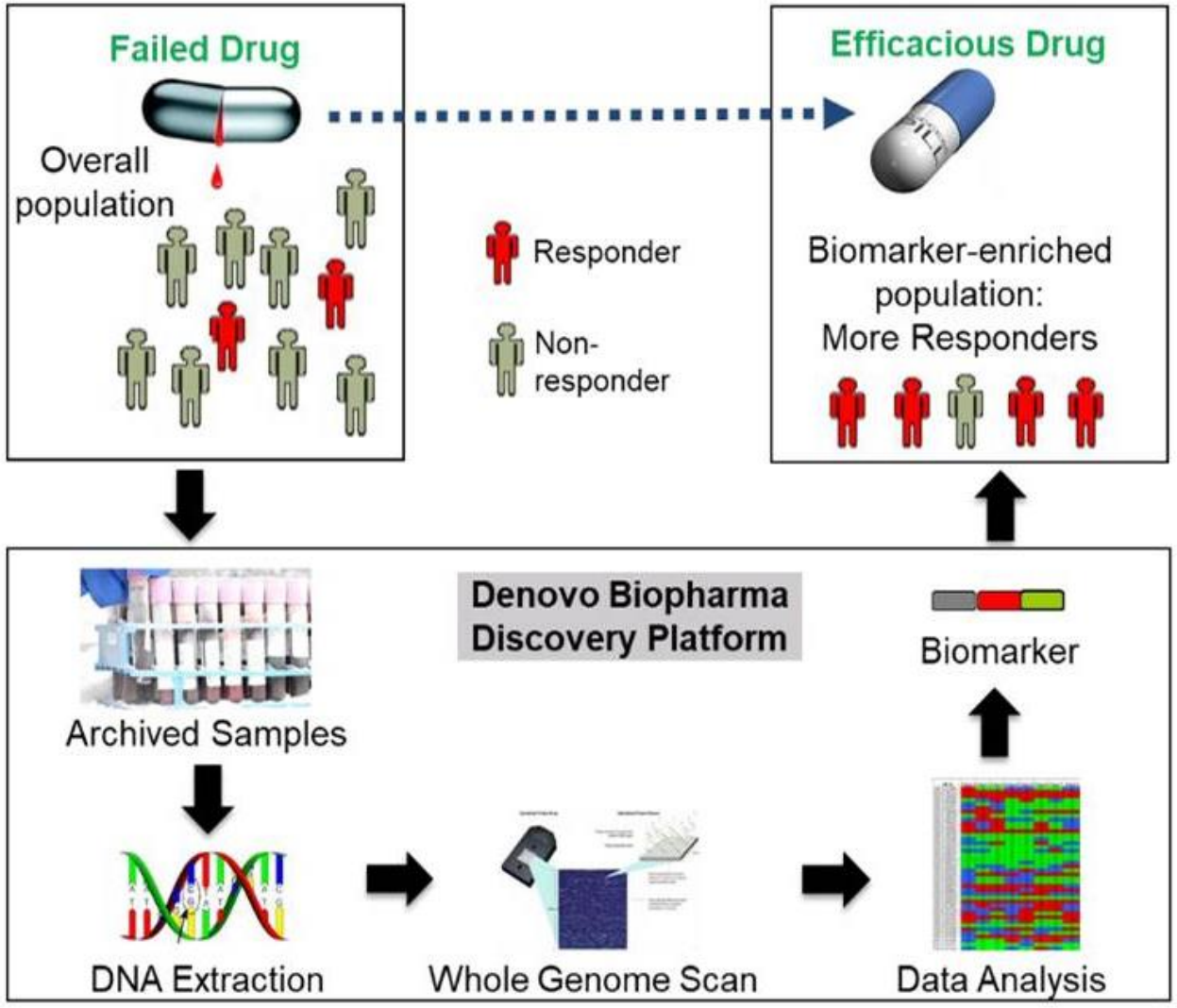


Mok 2009

A Biomarker (EGFR Mutation) Converted a Failed Drug into a Successful Precision Medicine

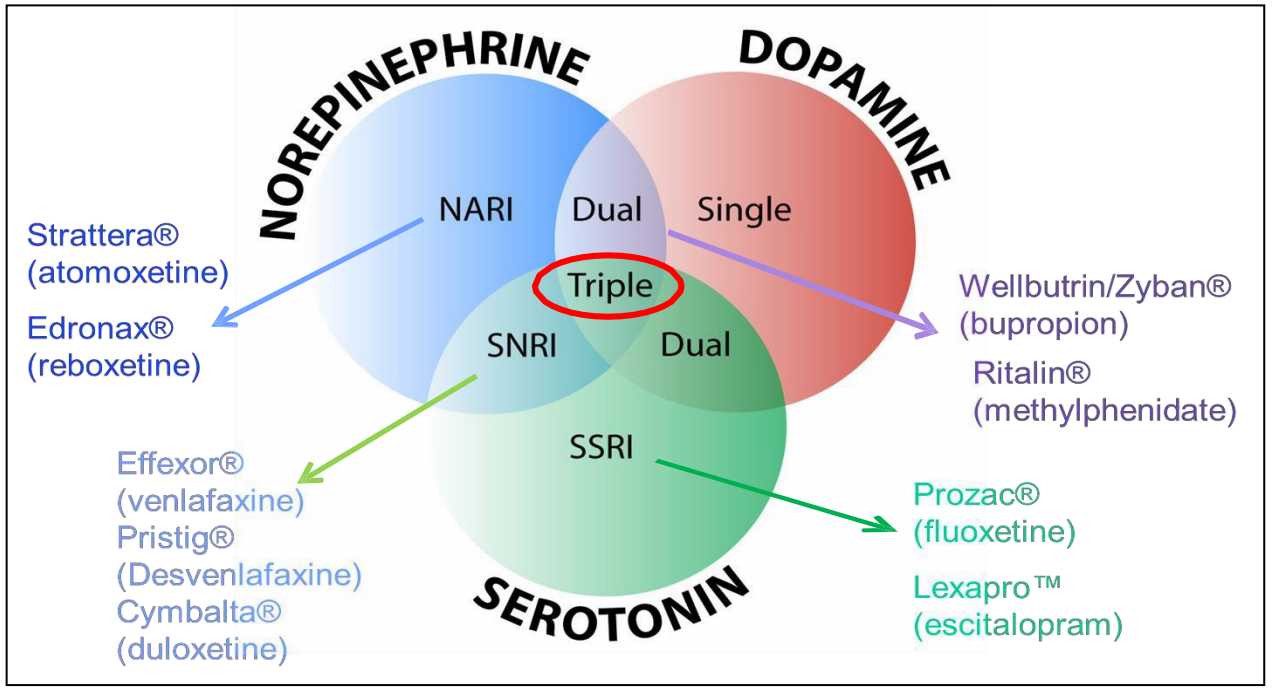
Our Unique Solution to Biomarker Discovery

Transforming Failed Drugs into Successful Personalized Medicines



- Proprietary sample processing procedure using archived patient plasma or other samples
- Proprietary data flow and data analysis algorithm
- Big data/machine learning to predict drug response
- Validation of plausible biomarkers by wet lab

Monoamine Reuptake Inhibitors for Depression: Why *not Target all Three Catecholamine Transporters?*



Augmentation of SSRI/SNRI with dopamine modulating therapies may provide improved and/or more rapid antidepressant effect

- Dopamine is involved in centrally-mediated reward responses
- Adding DAT inhibition has potential to offset side effects commonly associated with SSRI/SNRI, *including loss of libido*

Liafensine: A Potent, Selective Inhibitor of SERT, NET and DAT

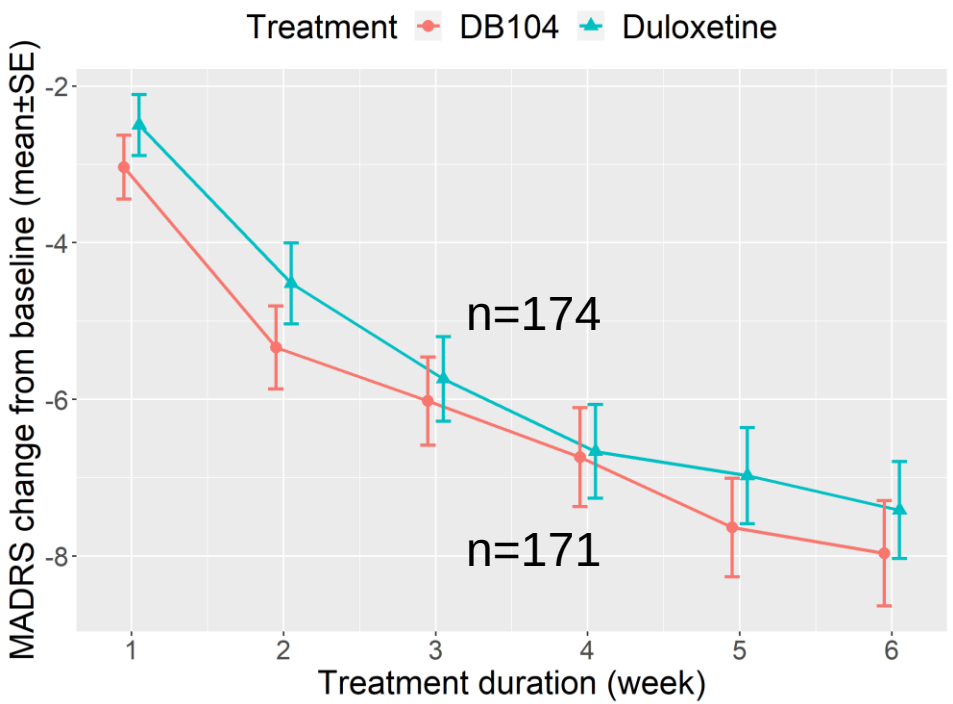
- Liafensine (DB104/AMR-000013/BMS-820836) : Potent selective, oral, once-daily, triple monoamine reuptake inhibitor; Binds serotonin (SERT) dopamine (DAT) and norepinephrine (NET) transporter in single nanomolar range (1 nM – 8nM)

- BMS assessed the clinical safety of liafensine in 14 completed studies, including 11 Phase 1 and 3 Phase 2 studies. Well tolerated in healthy volunteers and treatment resistant depression (TRD) patients

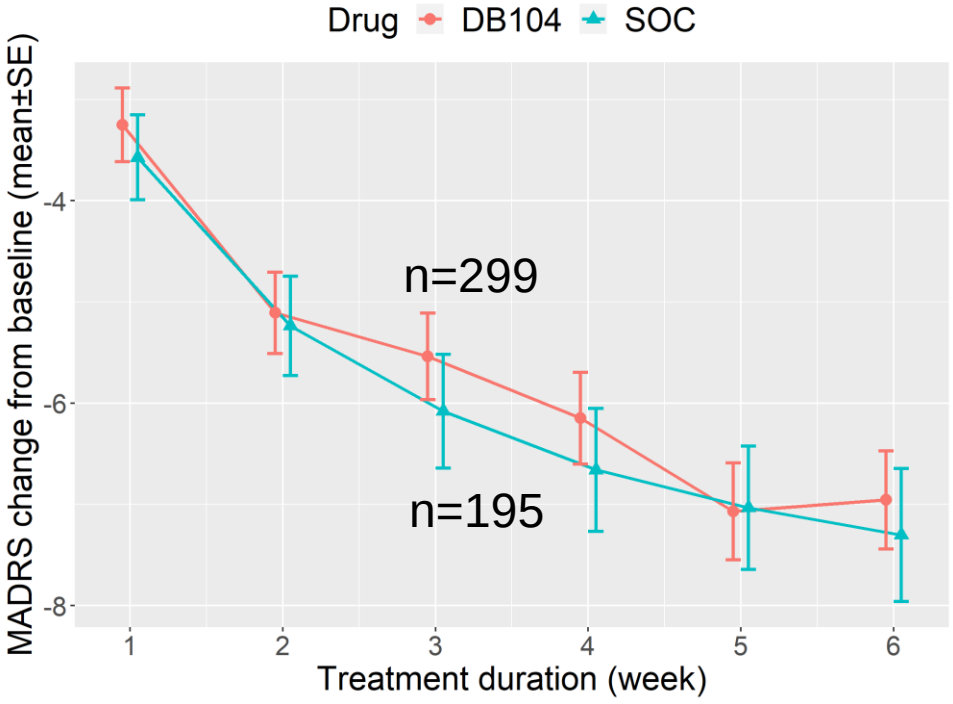
- The efficacy of liafensine in TRD was evaluated in two phase 2 studies: CN162006 and CN162007

Two BMS Phase 2b Studies Failed to Demonstrate Liafensine's (DB104) Efficacy Comparing to SOC

Study CN162-006

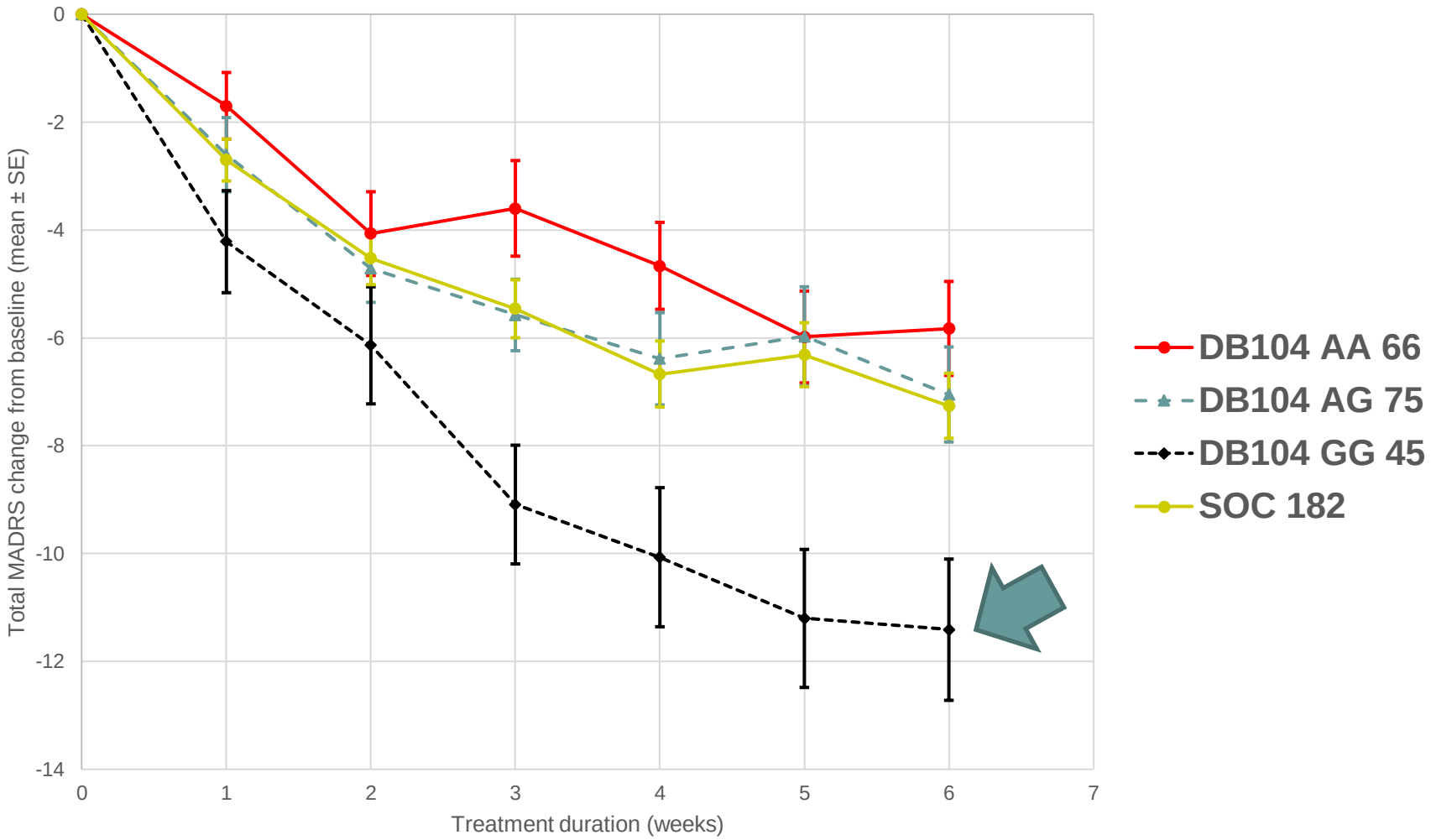


Study CN162-007



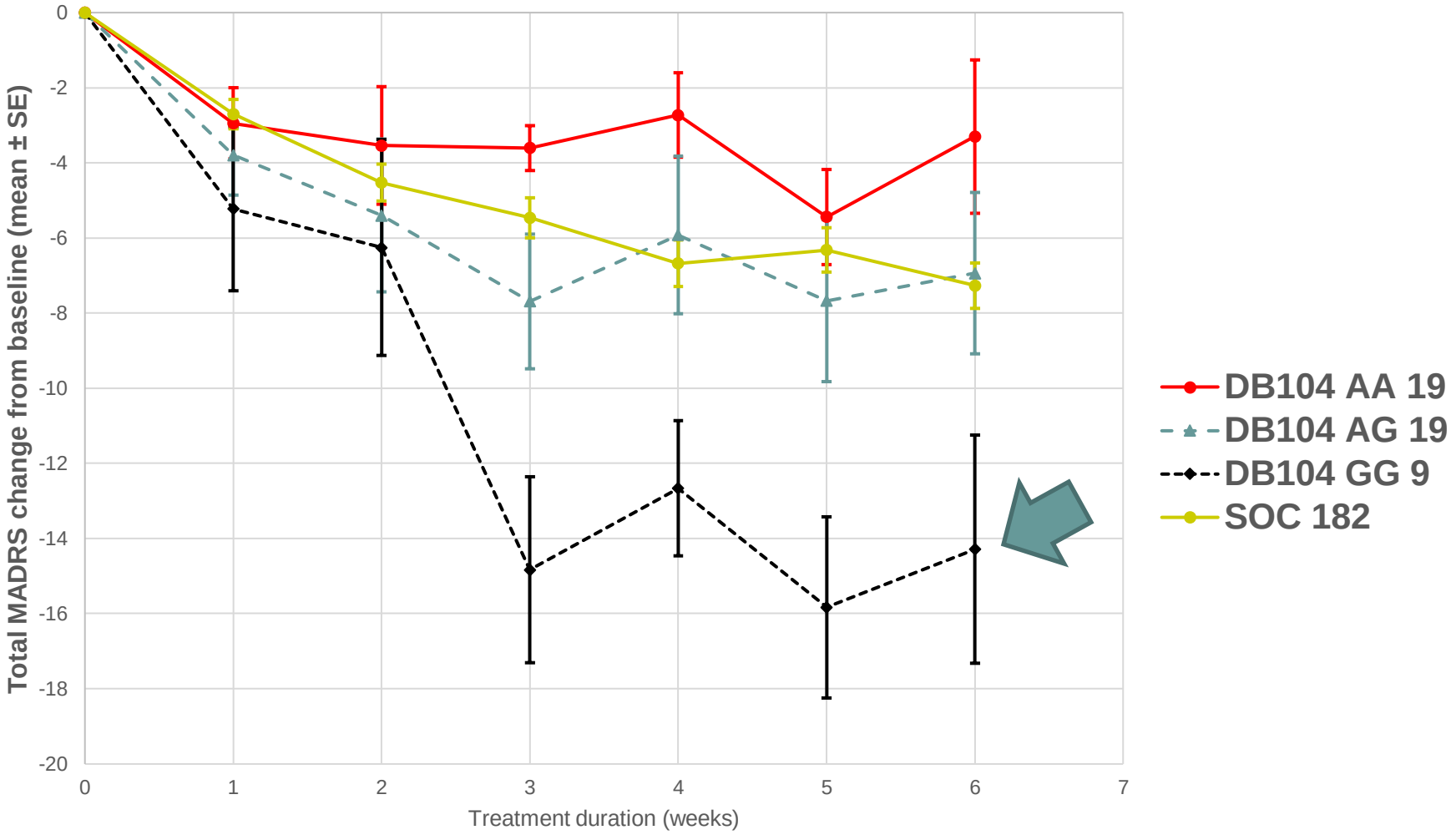
No apparent difference between Liafensine and SOC

DGM4 Biomarker Discovery Set: MADRS Score Change by DGM4 Genotypes



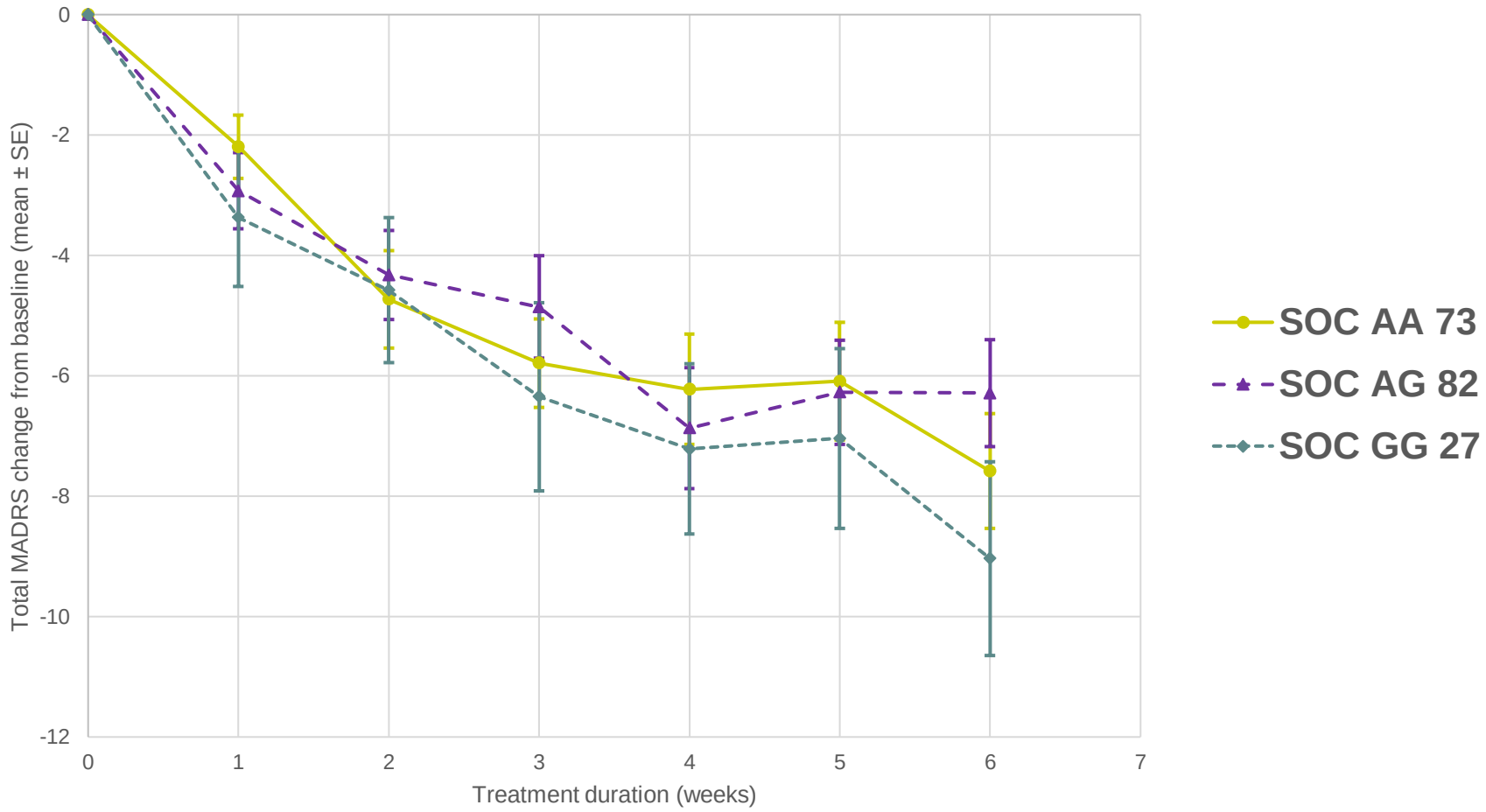
Patients with GG exhibited better efficacy vs those with AA or AG in Liafensine arm and SOC arm

Biomarker DGM4 Validation Set: MADRS Score Change by DGM4 Genotypes



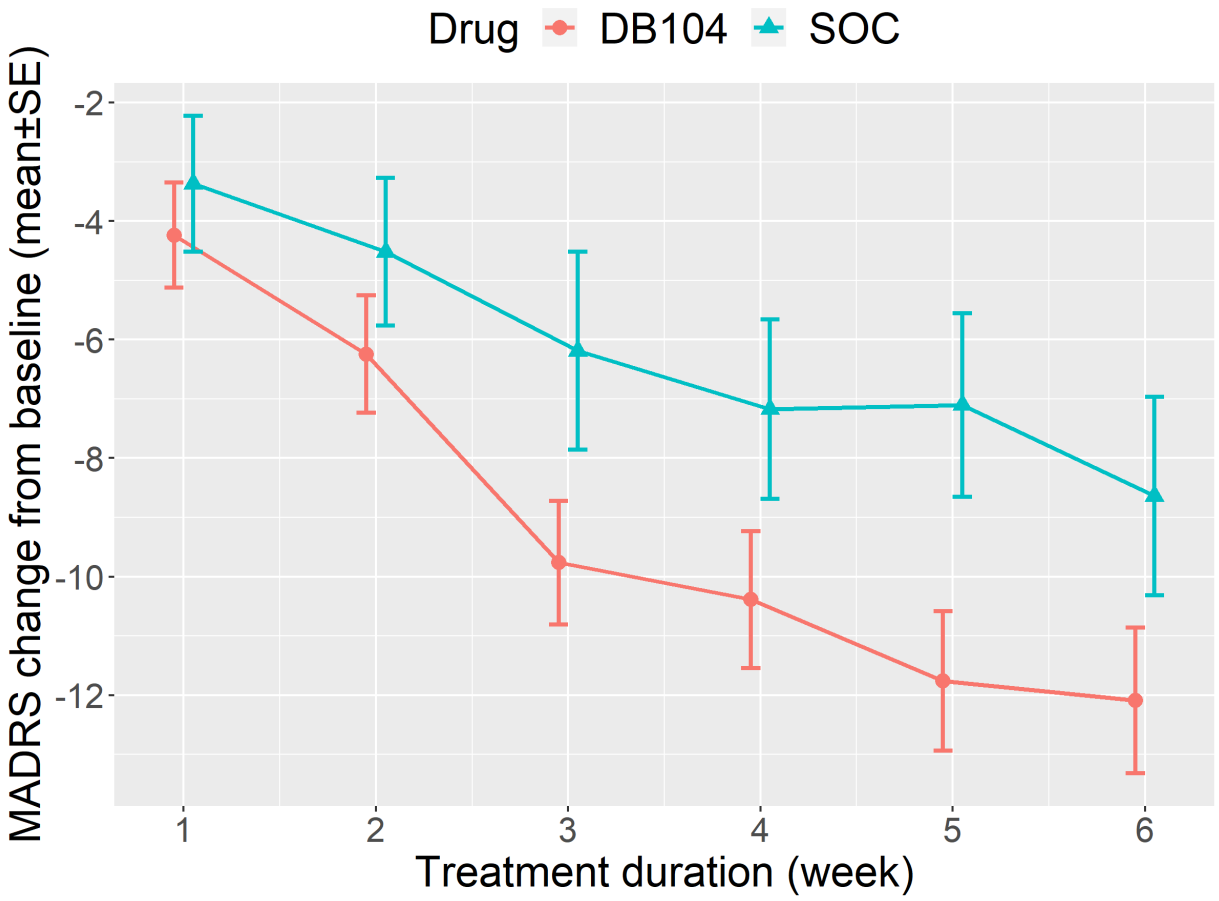
Discovery Set results were replicated in this validation set

MADRS Score Change by DGM4 Genotypes in Control Arm (SOC: Duloxetine/Escitalopram)



DGM4 is a specific biomarker for liafensine, not for SOC
Not a prognostic biomarker for TRD

Comparison of Liafensine (DB104) vs SOC in TRD Patients with GG Genotype (DGM4+)



SOC (standard of care): Duloxetine/Escitalopram

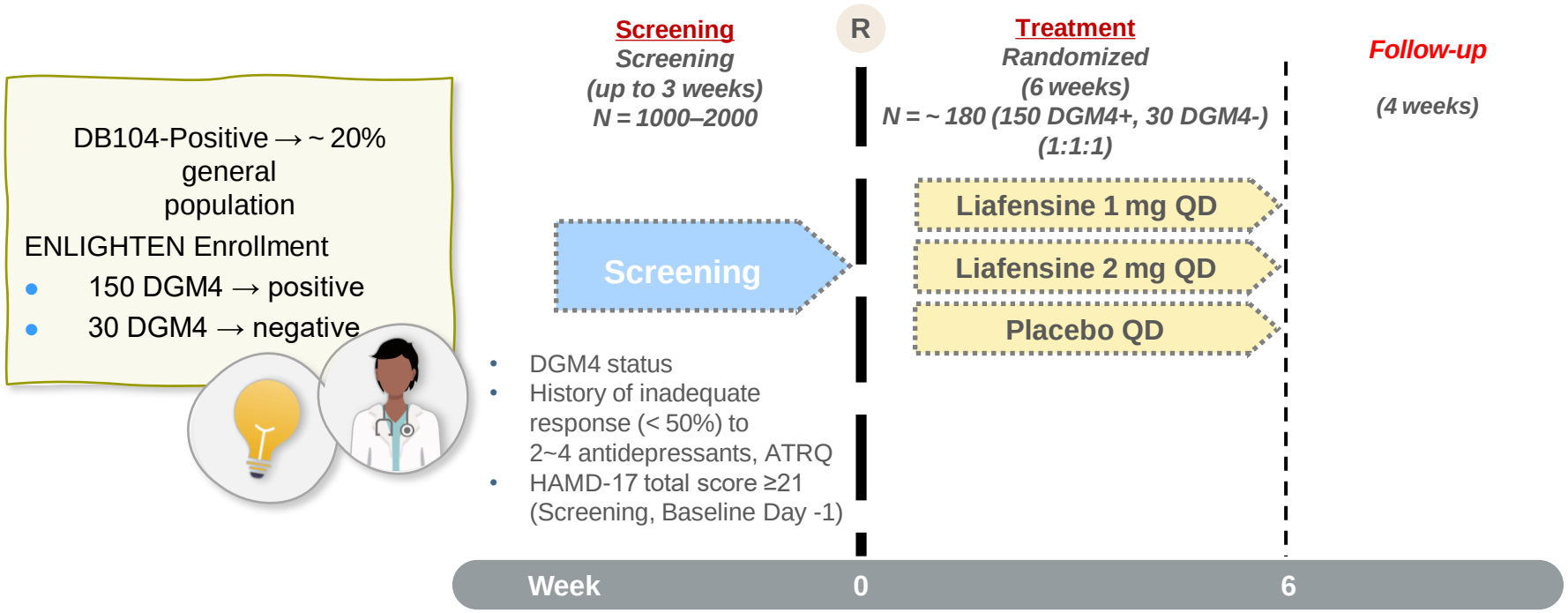
Drug	Patients (n)
SOC	27
Liafensine	54

(p = 0.02)

Prevalence of DGM4+ GG Biomarker in Different Ethnic Groups

Ethnicity/Region	DGM4-positive (%)
Eastern Asia	21.4
European	18.1
Puerto Rican	9.6
Mexican descend	4.7
African Ancestry	1.6

A Prospective Global Phase 2b Study:
A Biomarker-Guided, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Liafensine in Patients with Treatment-Resistant Depression - ENLIGHTEN



Countries: US, China, Canada
Number of subjects enrolled: 180 (5:1 DGM4+ to DGM4- ratio)
Number of sites: 54

ENLIGHTEN Objectives and Endpoints

Efficacy — Focus on DGM4-positive TRD subjects — Baseline to Day 42

Primary

- To demonstrate DB104 is superior to placebo — MADRS

Secondary

- Global severity — CGI-S
- Global improvement — CGI-I
- Disability assessment — SDS

Exploratory

- Response rate — MADRS ≥ 50% improvement
- Remission rate — MADRS ≤ 10
- Others

Safety

- Adverse events, laboratory findings, vital signs

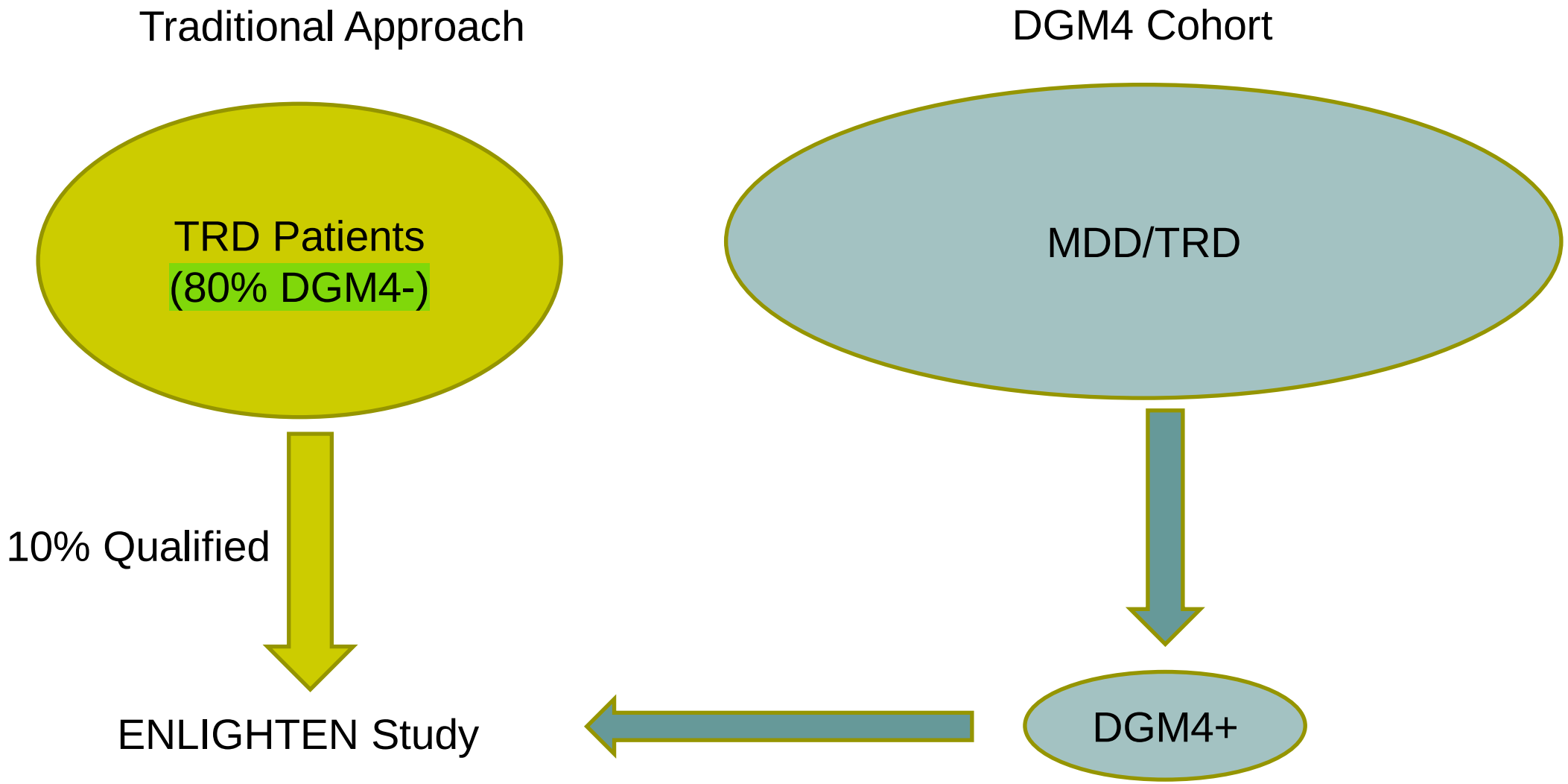
ENLIGHTEN: Conducted in more than 50 Clinical Centers

- A Global Phase 2b Study
  - US: 38 Sites
  - Canada: 3 Sites
  - China: 16 Sites

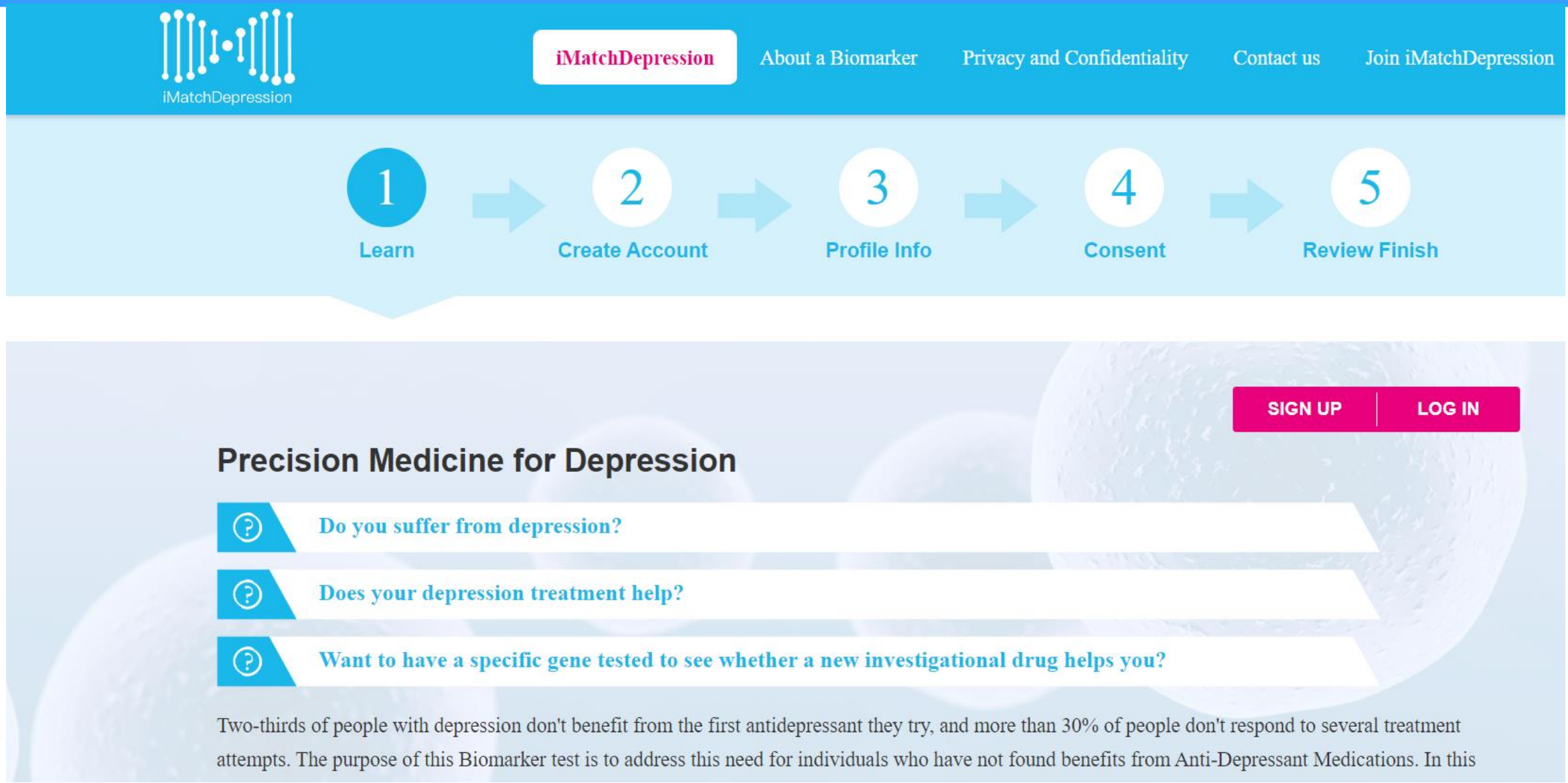
Challenges in Biomarker Guided Study – High Screen Failure Rate

- Total Screened: 1967 Patients
  - Screen Failed: 1788 Patients (91%)
  - Enrolled: 197 Patients

To Overcome Enrollment Challenge: DGM4 Cohort Program



Gene Registry: Biomarker Testing at Home



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Thank You

Questions?