Precision Medicine in non-Oncology therapeutic areas

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Need for new medicines

Cancers – 42%

Respiratory – 9%

Cardiovascular – 22%

%-ages refer to the premature death toll by each of those conditions

From: http://www.nhs.uk/Livewell/over60s/Pages/The-top-five-causes-of-premature-death.aspx

The 5R framework has guided scientific rigor to ask the ‘killer’ questions

Identifying the **right target**

Making sure our molecule gets to the **right tissue** where it is needed

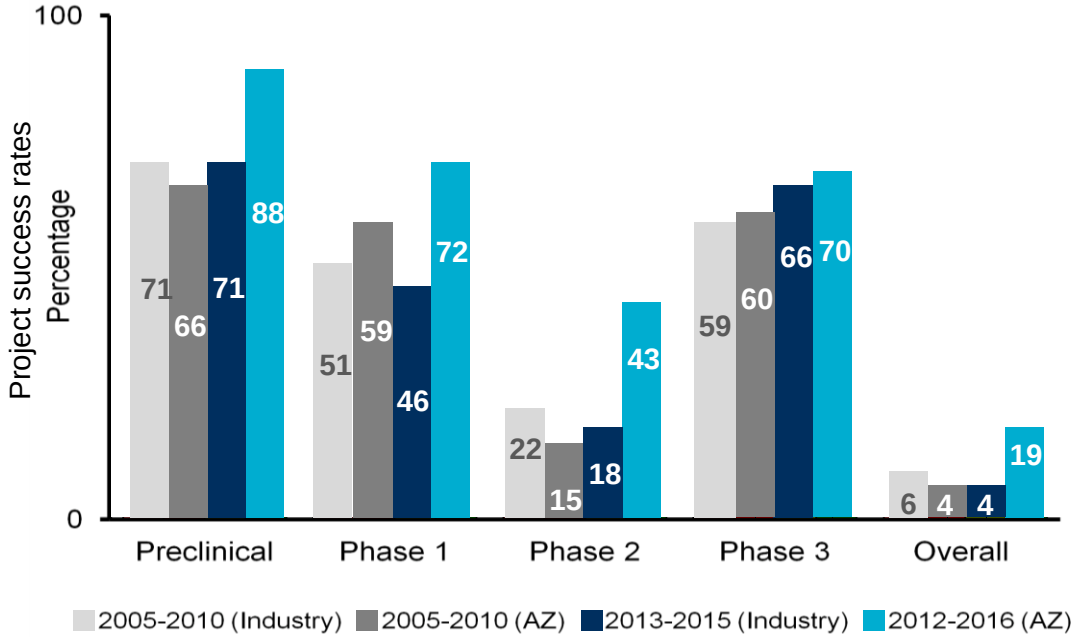
Ensuring **right safety** with minimal side effects

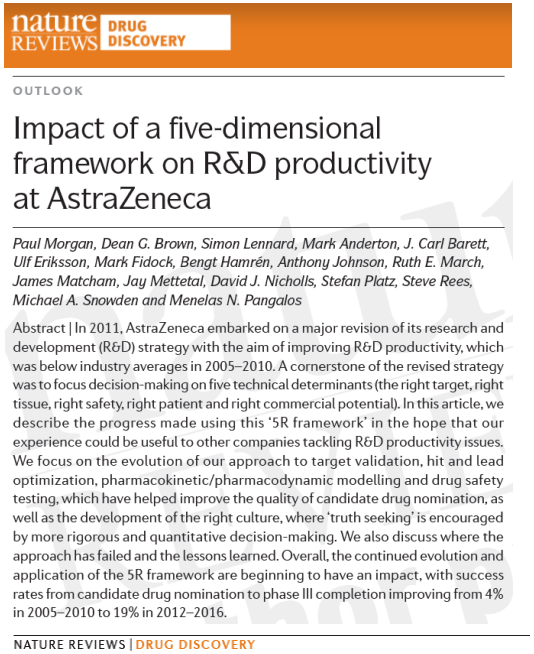
Selecting the **right patients** that will benefit

Defining the **right commercial** value and future viability

Underpinned by the **right culture** of truth-seeking behaviours and scientific rigor

As a result, we have delivered >4-fold improvement in AstraZeneca success rates from pre-clinical to Phase 3 completion since 2012





nature REVIEWS DRUG DISCOVERY

OUTLOOK

Impact of a five-dimensional framework on R&D productivity at AstraZeneca

Paul Morgan, Dean G. Brown, Simon Lennard, Mark Anderton, J. Carl Barrett, Ulf Eriksson, Mark Fidock, Bengt Hamrén, Anthony Johnson, Ruth E. March, James Matcham, Jay Mettetal, David J. Nicholls, Stefan Platz, Steve Rees, Michael A. Snowden and Menelas N. Pangalos

Abstract | In 2011, AstraZeneca embarked on a major revision of its research and development (R&D) strategy with the aim of improving R&D productivity, which was below industry averages in 2005–2010. A cornerstone of the revised strategy was to focus decision-making on five technical determinants (the right target, right tissue, right safety, right patient and right commercial potential). In this article, we describe the progress made using this '5R framework' in the hope that our experience could be useful to other companies tackling R&D productivity issues. We focus on the evolution of our approach to target validation, hit and lead optimization, pharmacokinetic/pharmacodynamic modelling and drug safety testing, which have helped improve the quality of candidate drug nomination, as well as the development of the right culture, where 'truth seeking' is encouraged by more rigorous and quantitative decision-making. We also discuss where the approach has failed and the lessons learned. Overall, the continued evolution and application of the 5R framework are beginning to have an impact, with success rates from candidate drug nomination to phase III completion improving from 4% in 2005–2010 to 19% in 2012–2016.

NATURE REVIEWS | DRUG DISCOVERY

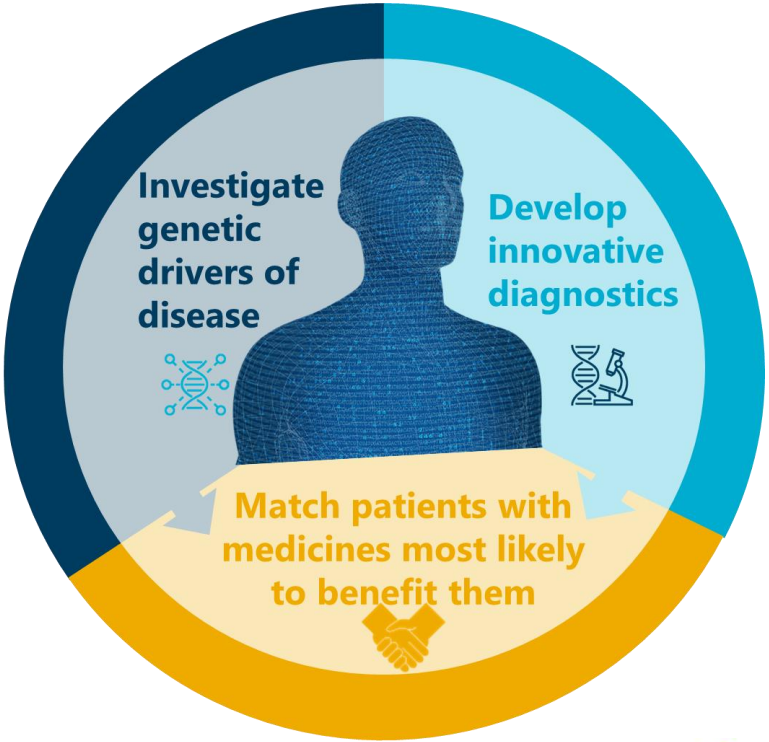
Morgan et al., 2018 *Nature Reviews Drug Discovery*

Precision medicine and genomics

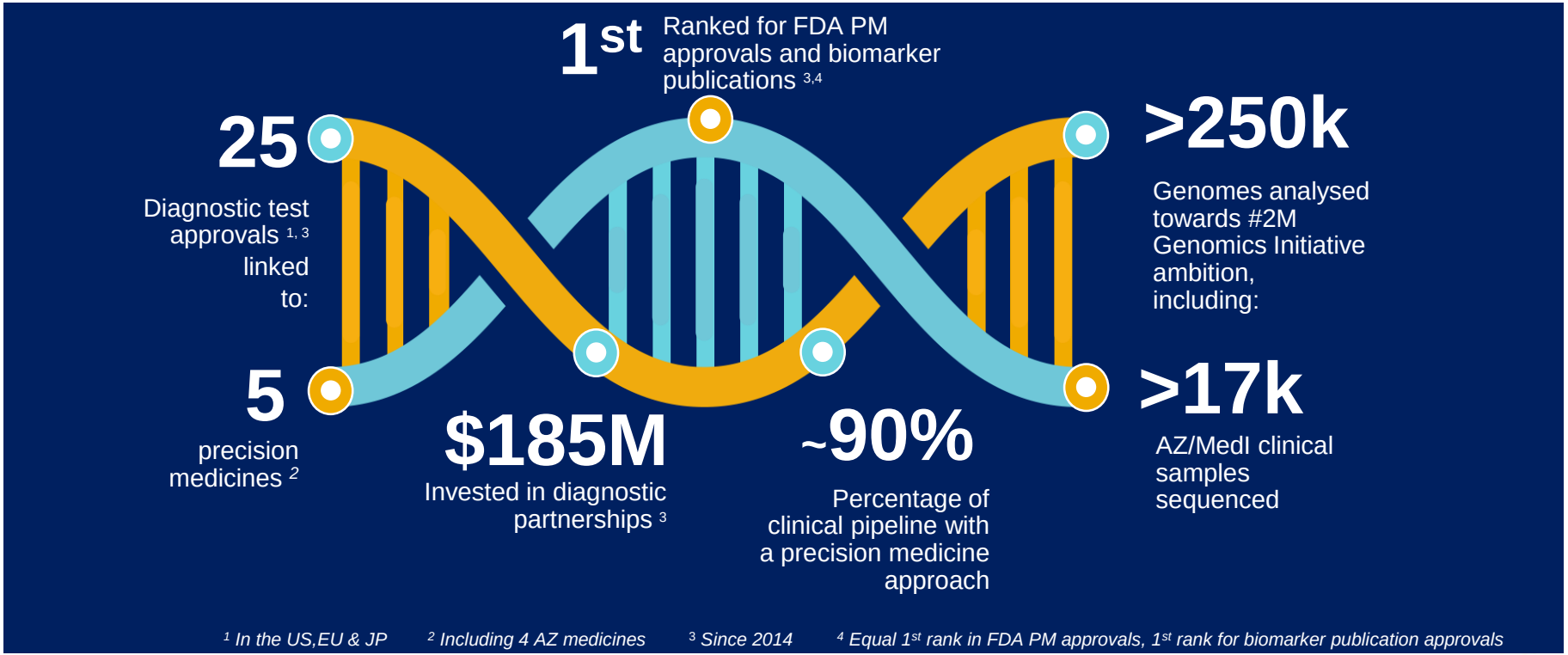
'The right patient'

We are driven by patient need, with a commitment to matching life-changing precision medicines to patients most likely to benefit

- across all our core therapeutic areas



Precision Medicine – it's in our DNA



1 In the US,EU & JP *2 Including 4 AZ medicines* *3 Since 2014* *4 Equal 1st rank in FDA PM approvals, 1st rank for biomarker publication approvals*

Approximately 90% of our NME clinical pipeline follows a Precision Medicine approach

~ 90% of our clinical pipeline follows a Precision Medicine approach, compared with 10% in 2009

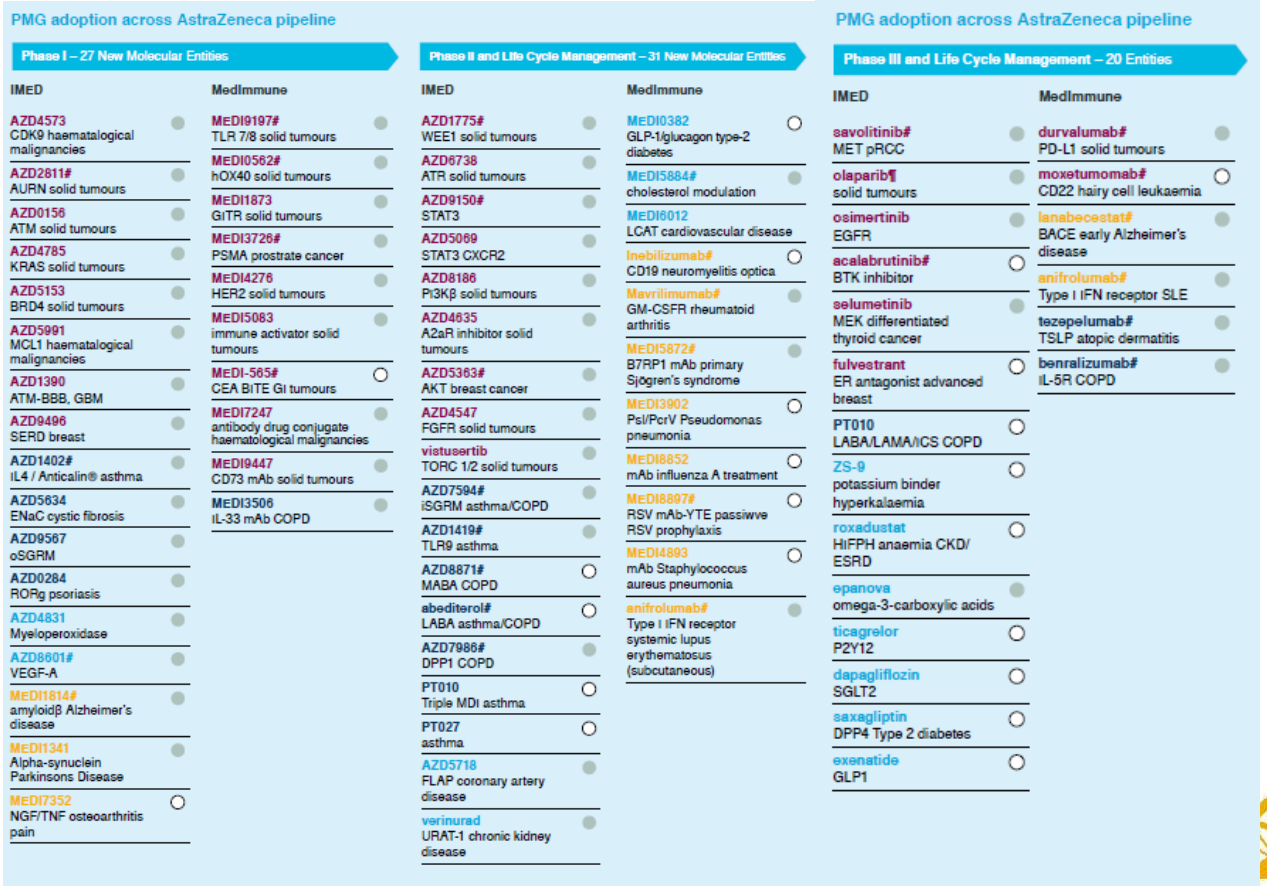
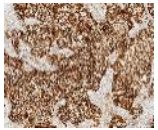


Figure from 2017 AZ IMED Annual Report

Diagnostics linked to four AZ medicines to guide therapy

Durvalumab
PD-L1 monoclonal antibody

PD-L1 complementary Dx (for Bladder - US)



Partner: Ventana

VENTANA
A Member of the Roche Group

Gefitinib
EGFR inhibitor

***EGFR* tissue (US) & plasma (EU)**
1st plasma CDx CE-IVD for solid tumour
Partner: Qiagen

QIAGEN

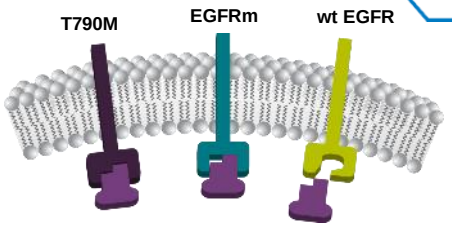
***EGFR* tissue & plasma US)** *Partner: RMS*

Roche

Osimertinib
Mutant-selective EGFR inhibitor

***EGFR T790M* tissue & plasma (US, EU, JPN)**
AZ's first FDA approved ctDNA test
***EGFRm* tissue & plasma (US, JPN)**
1st concurrent CDx tissue & plasma
Partner: RMS

Roche



***EGFR T790M* tissue NGS panel (US)**
Partner: FMI

FOUNDATION MEDICINE

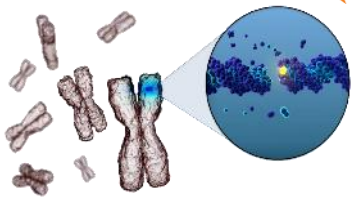
Olaparib
PARP inhibitor

Germline *BRCA* (US, EU, JPN)
Partner: Myriad
1st BRCA LTD CDx

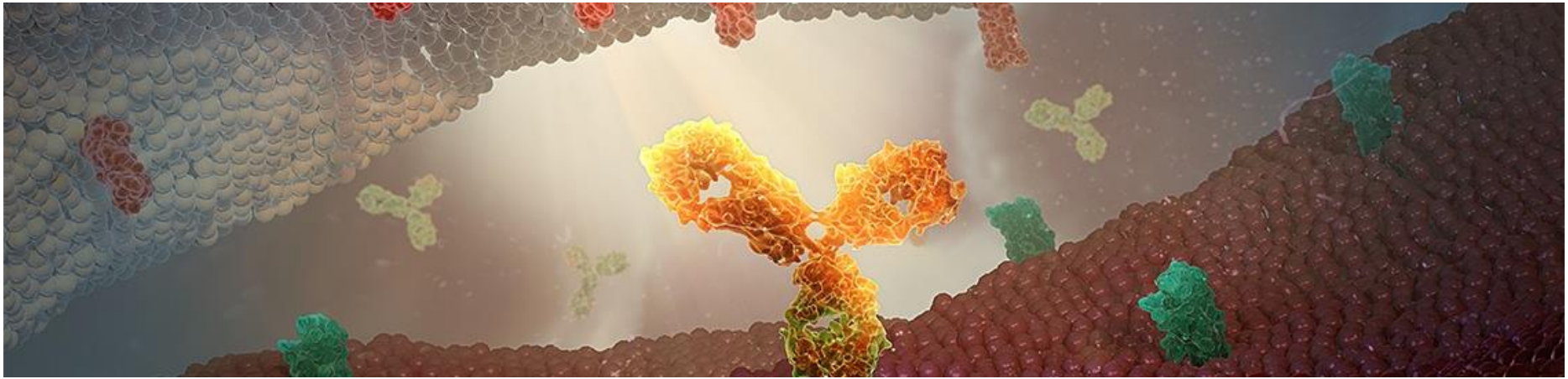
MYRIAD

Tumour *BRCA* CE IVD (EU)
Partners: Myriad, Multiplicom, Qiagen

MYRIAD QIAGEN Multiplicom
A part of Agilent Technologies



So what about Precision Medicine in non-Oncology areas?



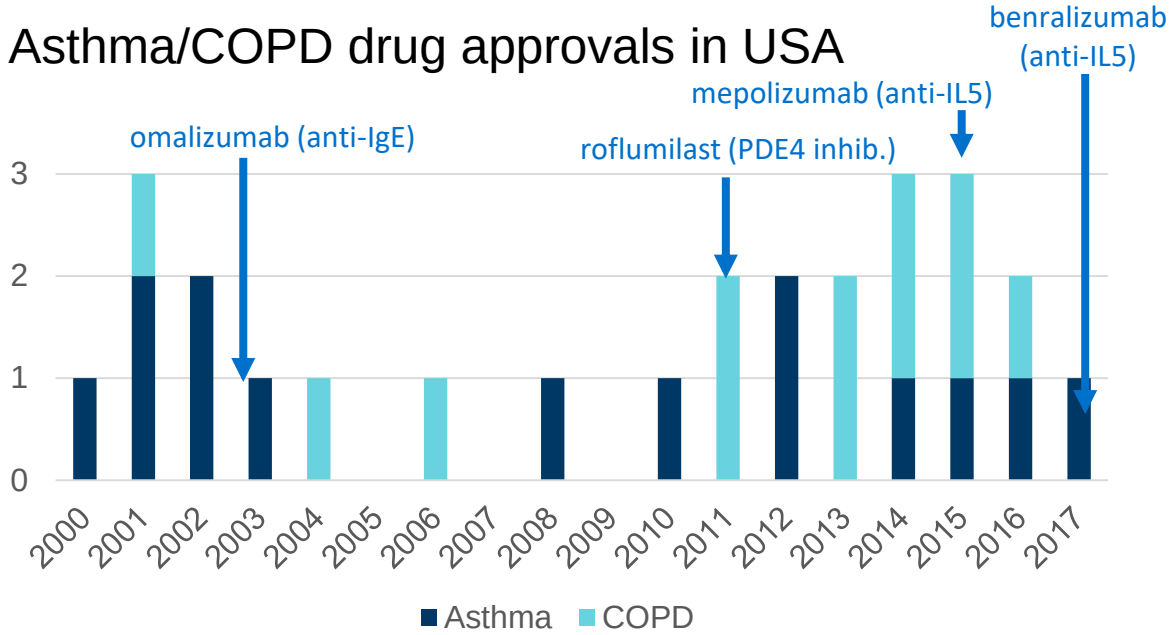
A diverse and exciting Precision Medicine portfolio

Oncology	Respiratory, Inflammation & Autoimmunity	Cardiovascular and Renal Metabolic
		
Immuno-oncology	Lung Immunity	Diabetes/NASH
DNA Damage Repair	Lung Epithelium	Heart Failure
EGFR/Lung	Lung Regeneration	Chronic Kidney Disease
Tumour drivers		
Haematology		

New drug approvals for asthma and COPD remain low

Only 3 novel mechanisms targeted in the last 17 years.

LABAs, LAMAs and corticosteroids still dominate new product launches

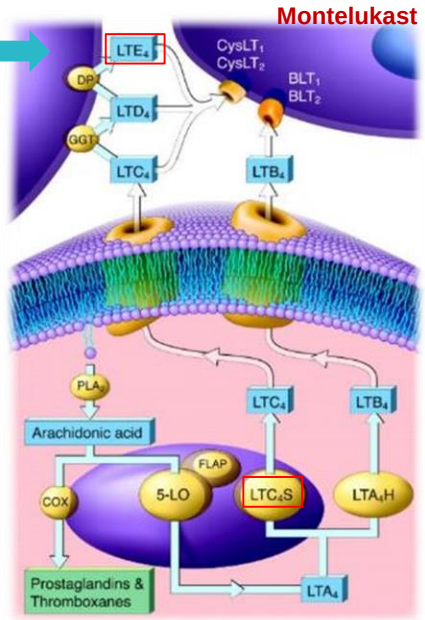


Sources: CenterWatch: FDA Approved Drugs for Pulmonary/Respiratory Diseases
FDA website: Novel Drug Approvals for 2017

How we could develop precision medicines to treat asthma?

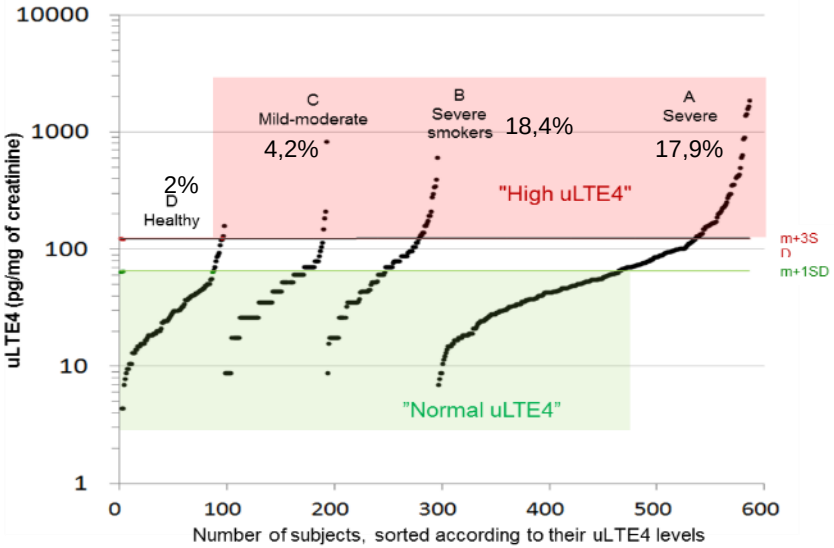
Cysteine leukotriene pathway clinically validated in asthma

Precision Medicine Biomarker



Hypothesis: patients most likely to benefit from LTC4S inhibition have CysLT activated pathway evidenced by high level of LTE4 (CysLT end product)

uLTE4 heterogeneity – discriminates between high/ low populations



uLTE4 data from U-BIOPRED cohort

Regardless of disease severity a significant number of asthmatics patients have ”high” LTE4 levels using arbitrary calculated threshold

Putting gout patients first – serum uric acid meter

HCPs and gout patients can now monitor uric acid which enables treatment to target uric acid levels, rather than to disease symptoms:

- First FDA cleared CLIA waived PoC test for serum uric acid (2017)
- First PoC test in a new FDA test category
  'home use by prescription'
- EU PoC certification achieved in 2016 and OTC approval in 2017

AstraZeneca's first FDA cleared point-of-care test

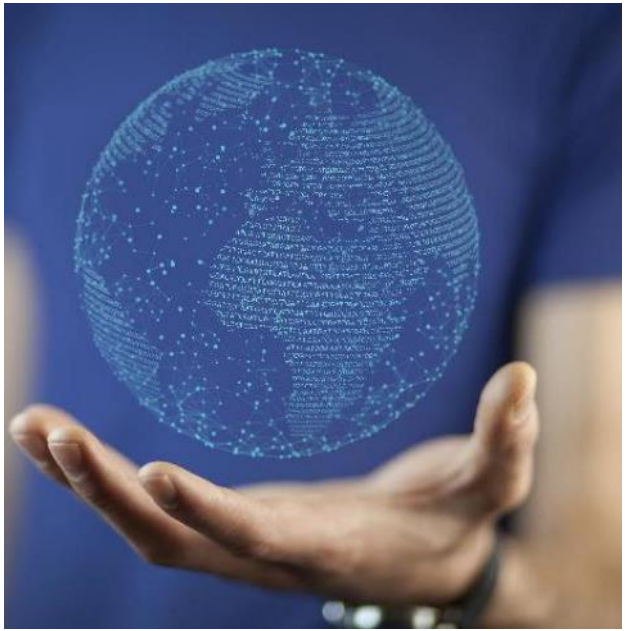
ONE drop of blood

Rapid sUA biomarker Test

Treatment management

The Power of Genomics

- Understand more about the biology of health and disease
- Identify new targets for medicines
- Support selection of patients for clinical trials
- Allow patients to be matched with treatments more likely to benefit them



The AstraZeneca and MedImmune Genomics Initiative

A company-wide Initiative, launched April 2016

2 million

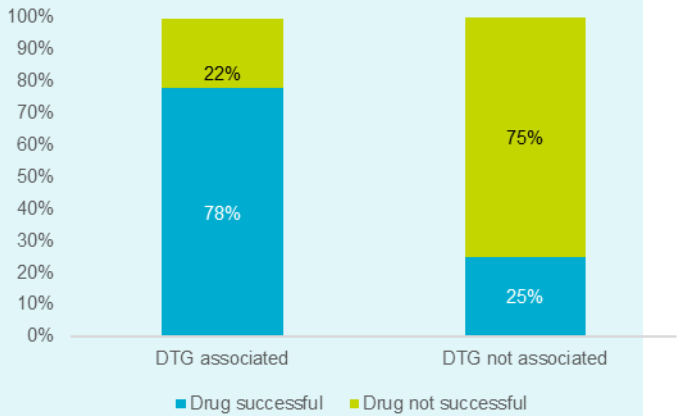
We have the bold ambition to analyse up to 2 million genomes by 2026

>500,000

This includes sequencing up to 500,000 genomic samples collected from our own clinical trials

Successful Genomics Proof of Concept study

Fig. 1. Drug target genes from successful drug programs have over 3-fold genetic associations compared with unsuccessful programs



Drug target genes associated with clinical phenotypes in the genetically isolated population of Finland more likely to succeed in pharmaceutical development; *March et al., 2017 Poster Presentation, ASHG*

ASHG2017
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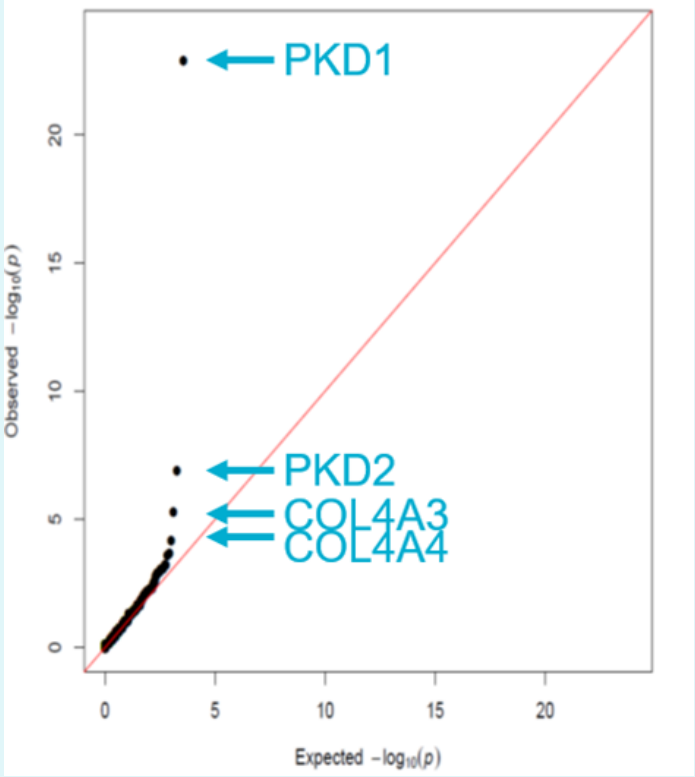
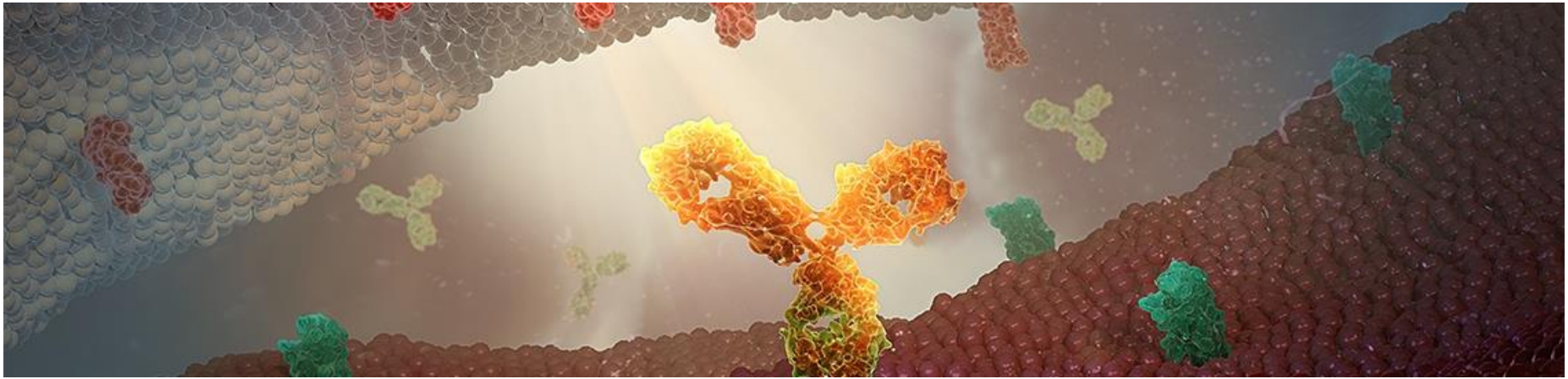
Collapsing analysis: Distribution of observed and expected P-values in non-synonymous variants (CKD)

Gene Name	Fet P
PKD1	**1.21E-23**
PKD2	**1.28E-07**
COL4A3	4.93E-06
COL4A4	6.58E-05



Hunting rare variants in chronic kidney disease
Cameron-Christie & Groopman et al

How can we further increase our success rate in Precision Medicine to benefit patients across all indications?



Successful precision medicine requires a diverse set of skills and collaboration – to benefit patients best

Understand **patients** and physicians needs

Availability of suitable **sample**

Develop **companion diagnostic** and approval

Continuous **biomarker science** & translation to clinic

Diversity of testing methods

Access to testing, 'finding' the patients and TAT

Test **reimbursement**

TAT, turn around time

Precision Medicine: the future is now

Recent

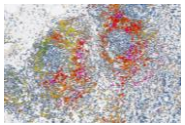
BRCA Companion Diagnostic

Circulating tumour DNA label

Single genes

Present

IO Diagnostic Solutions



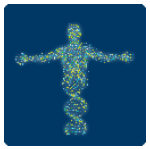
Multigene DNA panels

Point-of-care Diagnostics (PoC)

Multigene panels & PoC

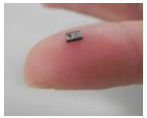
Future

Genomics & other ‘-omics’



Early diagnosis and monitoring

Sensors

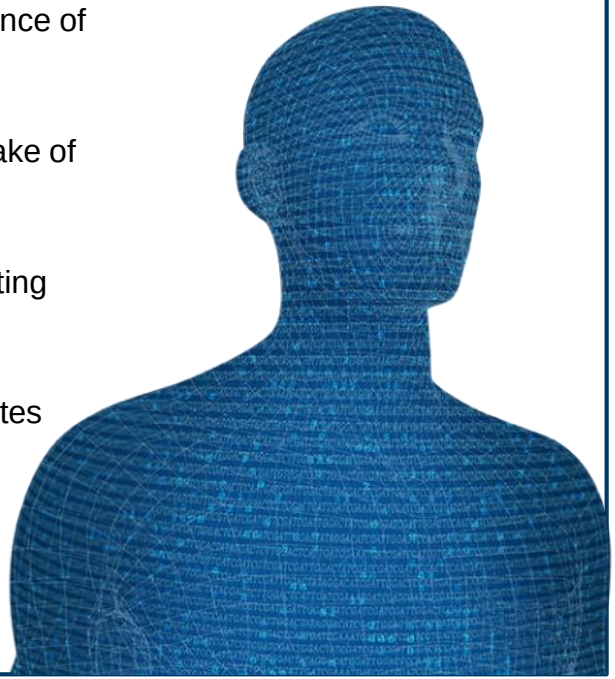


Artificial intelligence

PoC Genomics & AI

Critical success factors to drive precision medicine for the benefit of patients and innovation

- **Pragmatic regulatory systems** enabling approval of emerging science of Precision Medicine
- **Supportive reimbursement environment** that accelerates the uptake of approved targeted therapies and linked diagnostics
- **Continued investment in technology** such as next-generation testing infrastructure (e.g., NGS, ctDNA) to drive diagnostic innovation
- **Coordinated health care delivery system** that continuously educates health care practitioners and empowers patients
- **Appropriate data sharing mechanisms** that harness the power of population-level genomic and clinical databases



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