Topics

✔ Precision Medicine and Companion Diagnostics

✔ Importance of Partnerships for Biomarkers and CDx

•   Definiens and Covance Partnership

✔ Tissue Phenomics

•   Applications for Immuno-Oncology
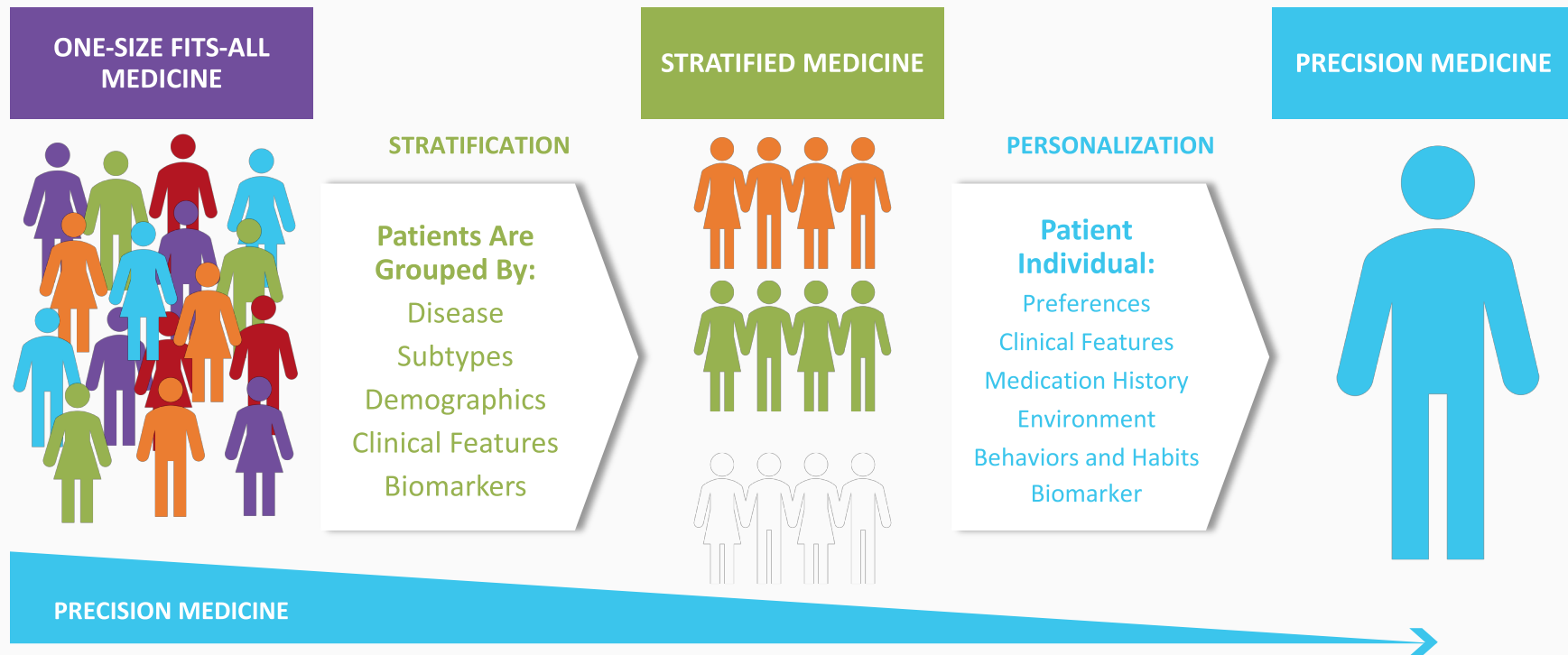
✔ Future Considerations

Precision Medicine and Companion Diagnostics

Drug Development and Precision Medicine

ONE-SIZE FITS-ALL MEDICINE

STRATIFIED MEDICINE

PRECISION MEDICINE

STRATIFICATION

Patients Are Grouped By:
Disease
Subtypes
Demographics
Clinical Features
Biomarkers

PERSONALIZATION

Patient Individual:
Preferences
Clinical Features
Medication History
Environment
Behaviors and Habits
Biomarker
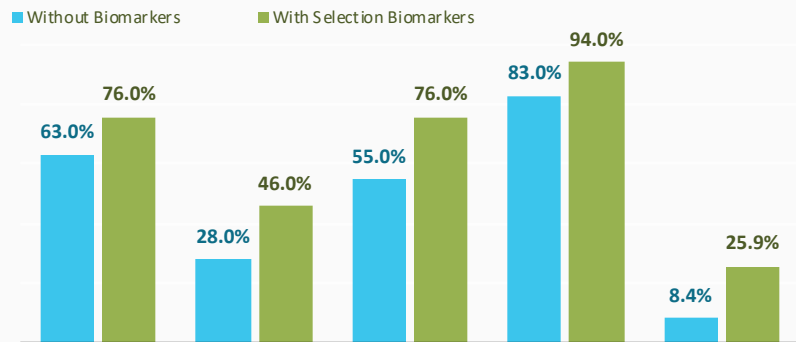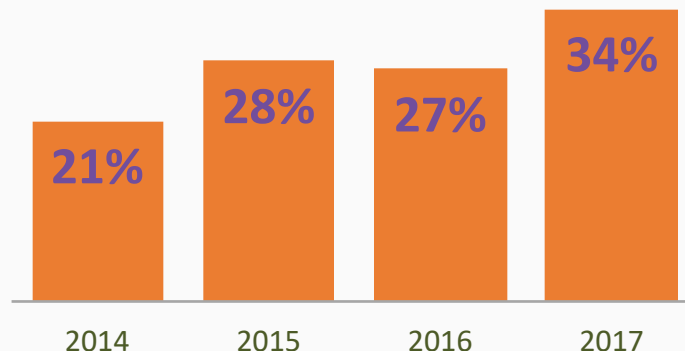
PRECISION MEDICINE

Source: Manchester Precision Medicine Institute

Biomarker Driven Programs Enhance Success

PROBABILITY OF SUCCESS WITH OR WITHOUT SELECTION BIOMARKERS

- ■ Without Biomarkers
- ■ With Selection Biomarkers

63.0% / 76.0%
28.0% / 46.0%
55.0% / 76.0%
83.0% / 94.0%
8.4% / 25.9%

PERSONALIZED MEDICINES TOP 30% OF FDA APPROVALS FOR FIRST TIME IN 2017

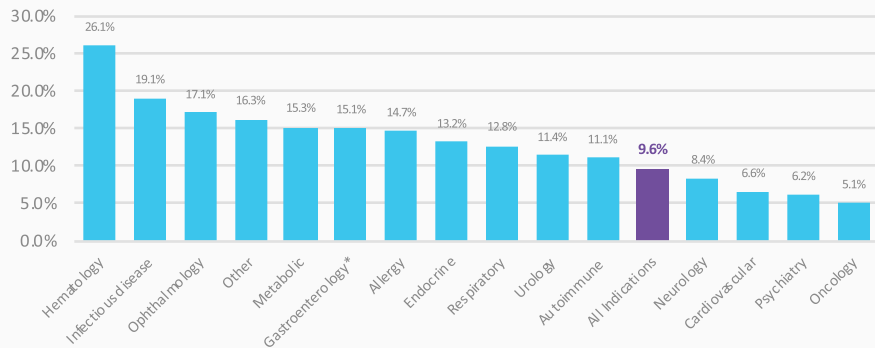| 2014	2015	2016	2017
21%	28%	27%	34%

BIOMARKERS ARE KEY FEATURES OF DEVELOPING NEW THERAPIES AND DIAGNOSTICS
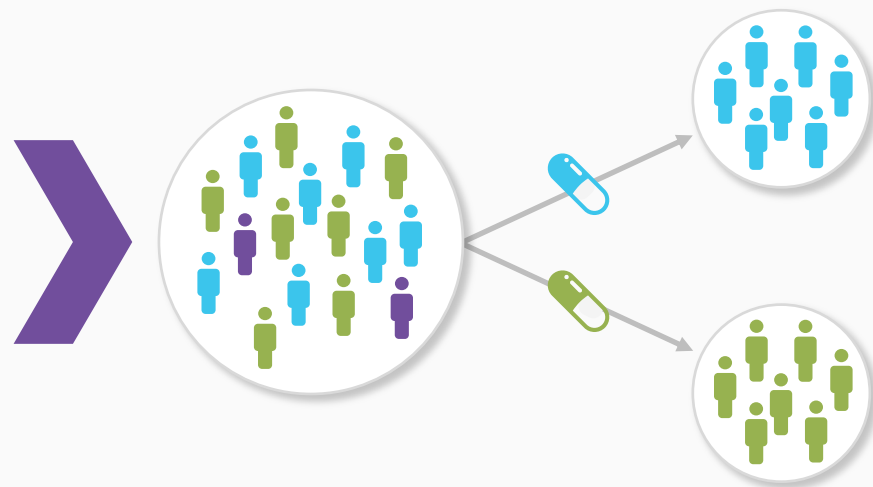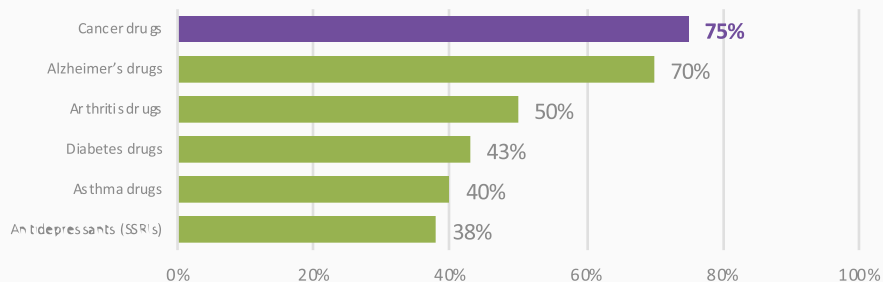
BIO, Biomedtracker, Amplion 2016.pdf. www.bio.org

▶ Deep knowledge of biology improves success
  ▶ Target/Mechanism/Biomarkers
▶ Evolution of new treatment modalities
  ▶ Gene and Cell based therapies
▶ Patient selection and stratification
  ▶ Biomarkers and Companion diagnostics

The Case for Companion Diagnostics

LIKELIHOOD OF APPROVAL FROM PHASE I

Hematology 26.1%
Infectious disease 19.1%
Ophthalmology 17.1%
Other 16.3%
Metabolic 15.3%
Gastroenterology* 15.1%
Allergy 14.7%
Endocrine 13.2%
Respiratory 12.8%
Urology 11.4%
Autoimmune 11.1%
All Indications 9.6%
Neurology 8.4%
Cardiovascular 6.6%
Psychiatry 6.2%
Oncology 5.1%

ONE SIZE DOES NOT FIT ALL
PATIENTS CAN RESPOND DIFFERENTLY TO THE SAME MEDICINE

Cancer drugs 75%
Alzheimer's drugs 70%
Arthritis drugs 50%
Diabetes drugs 43%
Asthma drugs 40%
Antidepressants (SSRIs) 38%

Partnership between Covance and Definiens

Partnership Established

- Definiens and Covance/Labcorp announced strategic partnership in Oct 2018
  - Covance
    - Leading pharma partner in clinical development
    - Strong CDx capabilities (IVD and ssPMA)
  - Labcorp
    - Touchpoints with 115m patients per year
  - Definiens
    - Tissue Phenomics® leader in supporting patient profiling

- Executive led partnership for clinical biomarker strategies and CDx services to pharma
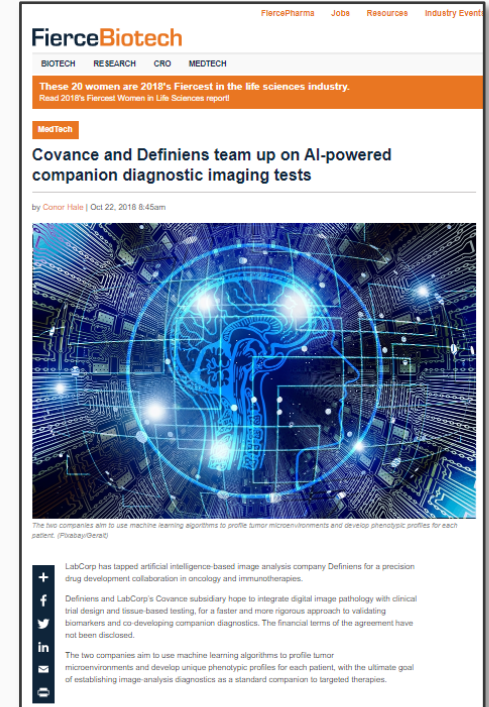
Applications for Tissue Phenomics

The Immune System and Cancer

Multiple approaches to immunotherapy in cancer

- Immune Checkpoint Inhibition
  - PD-1/PD-L1
- Immune System Activators
  - OX-40
- Adoptive T Cell Transfer
  - CAR-T
- Cancer Vaccines
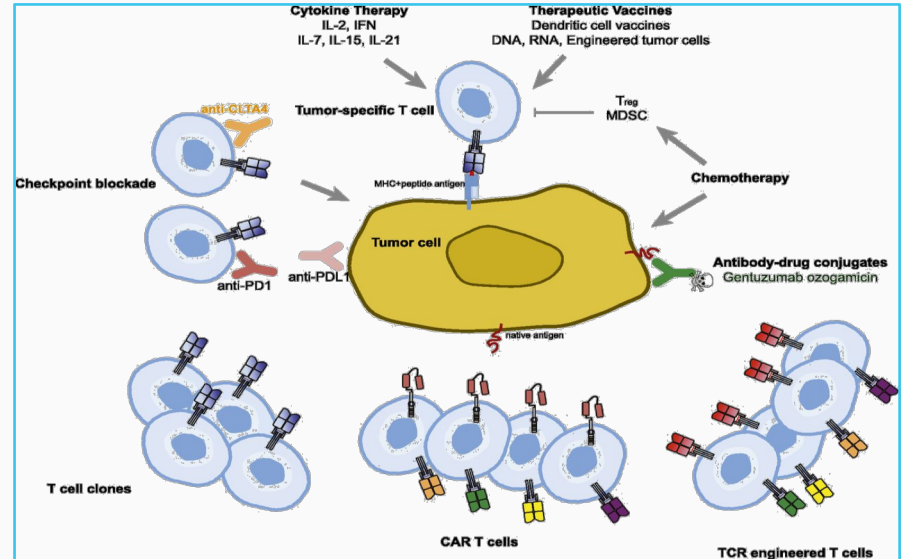
Marcela V. Maus et al. Blood 2014

Current Challenges in Immuno-Oncology Drug Development

- Highly competitive landscape
  - Number of companies, approaches and molecules in development
- Availability of appropriate patients
  - Increasing number of trials, with demand for specific enrollment
- Appropriate preclinical models
- Which biomarker(s) should be considered
  - Cell, Tissue, Genomic biomarkers
- Incorporation of appropriate trial design and execution strategy

Patient Profiling

The Power of Tissue Phenomics®
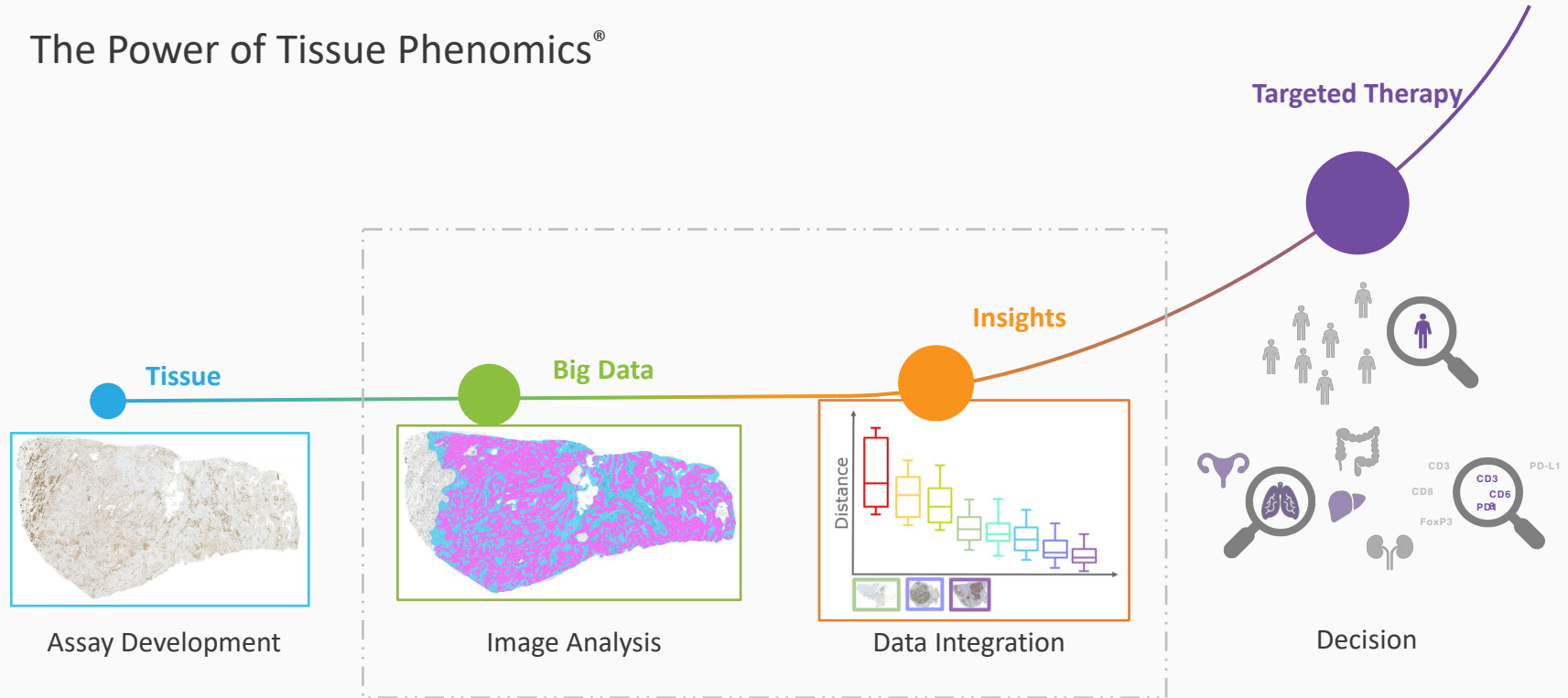
Scientific rationale – Why tissue?

Unique information in intact tissue

- PD-L1 remains key in IO

- Location of cells matters:
  Tumor resident and circulating peripheral immune cells are distinct populations1

- Spatial relationships between cell populations matter: Context of cellular localization is critical to understand biology & MoA2

- Tumor heterogeneity matters: TME is heterogenous and a modulator of tumor cell states3,4,5

Genomic information has limitations

- TMB has limitations: PD-L1 scores in NSCLC patients can be (or is) heterogeneous, therefore quantifications by IHC can overcome challenges in therapeutic decisions6

- Mutational Density does not give the whole picture: little correlation with Presence of the infiltrated T cells7
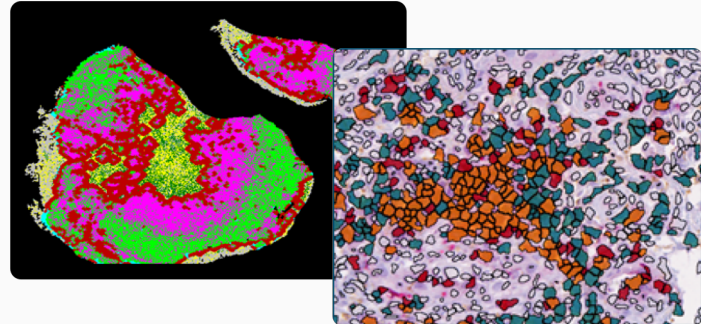
REFERENCES
1) Azizi, E et al. (2018). Single-Cell Map of Diverse Immune Phenotypes in the Breast Tumor Microenvironment. Cell
2) Malta, T.M., et al. (2018). Machine Learning Identifies Stemness Features Associated with Oncogenic Dedifferentiation. Cell
3) Lambrechts, D et al. (2018). Phenotype molding of stromal cells in the lung tumor microenvironment.
 Nature Medicine
4) Webinar Data Moritz Widmaier DEFINIENS AG
5) Lenos, K.J., et al. (2018). Stem cell functionality is microenvironmentally defined during tumour expansion and therapy response in colon cancer. Nature Cell Biology
5) Jamal-Hanjani, et al. (2017). Tracking the Evolution of Non–Small-Cell Lung Cancer. New England Journal of Medicine
6) Yoneshima, Y et al. (2018) PD-L1 expression in lung adenocarcinoma harboring EGFR mutations or ALK rearrangements.
7) Spranger S., et al. Density of immunogenic antigens does not explain the presence or absence of the T-cell–inflamed tumor microenvironment in melanoma
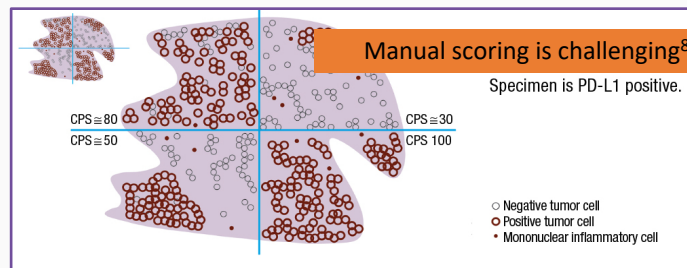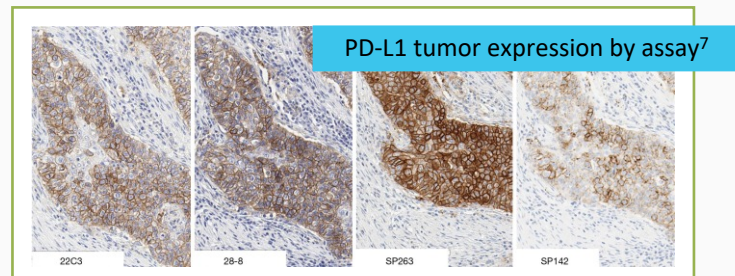
Improving PD-L1 scoring

Challenges

▸ Assays for PD-L1 assessment are diverse [1]

▸ Manual scoring is time consuming and challenging [1]

▸ Mapping of assays, cut-off values and therapies is complicated and highly dynamic [2, 3]

Solution

▸ Standardization supported with Image Analysis (IA) [3, 4]

▸ Oncologists can receive latest mapping of PD-L1 status to eligible treatments with automated solution [5, 6]

PD-L1 tumor expression by assay[7]

22C3   28-8   SP263   SP142

Manual scoring is challenging[8]

Specimen is PD-L1 positive.

CPS≅80   CPS≅30
CPS≅50   CPS 100

○ Negative tumor cell
◉ Positive tumor cell
• Mononuclear inflammatory cell

REFERENCES
1) Tsao, M.S., Kerr, K.M., Kockx, M., Beasley, M.-B., Borczuk, A.C., Botling, J., Bubendorf, L., Chirieac, L., Chen, G., Chou, T.-Y., et al. (2018). PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of Blueprint phase 2 project. Journal of Thoracic Oncology.
2) Mino-Kenudson, M. (2016). Programmed cell death ligand-1 (PD-L1) expression by immunohistochemistry: could it be predictive and/or prognostic in non small cell lung cancer? Cancer Biol Med 13, 157–170.
3) McLaughlin, J., Han, G., Schalper, K.A., Carvajal-Hausdorf, D., Pelekanou, V., Rehman, J., Velcheti, V., Herbst, R., LoRusso, P., and Rimm, D.L. (2016). Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non–Small-Cell Lung Cancer. JAMA Oncol 2, 46–54.
4) Udall, M., Rizzo, M., Kenny, J., Doherty, J., Dahm, S., Robbins, P., and Faulkner, E. (2018). PD-L1 diagnostic tests: a systematic literature review of scoring algorithms and test-validation metrics. Diagnostic Pathology 13, 12.
5) Teng, F., Meng, X., Kong, L., and Yu, J. (2018). Progress and challenges of predictive biomarkers of anti PD-1/PD-L1 immunotherapy: A systematic review. Cancer Letters 414, 166–173.
6) Tsao, M.-S., Le Teuff, G., Shepherd, F.A., Landais, C., Hainaut, P., Filipits, M., Pirker, R., Le Chevalier, T., Graziano, S., Kratze, R., et al. (2017). PD-L1 protein expression assessed by immunohistochemistry is neither prognostic nor predictive of benefit from adjuvant chemotherapy in resected non-small cell lung cancer. Annals of Oncology mdx003.
7) Mathew, M., Safyan, R.A., and Shu, A.C. (2017) PD-L1 as a biomarker in NSCLC: challenges and future directions. Ann Transl Med. 2017 Sep; 5(18): 375.
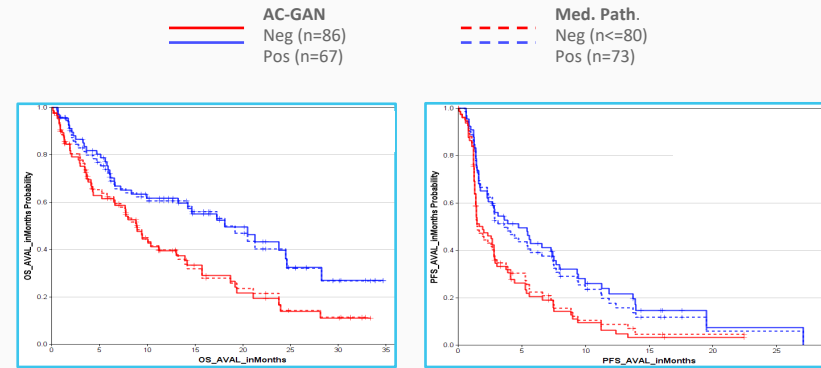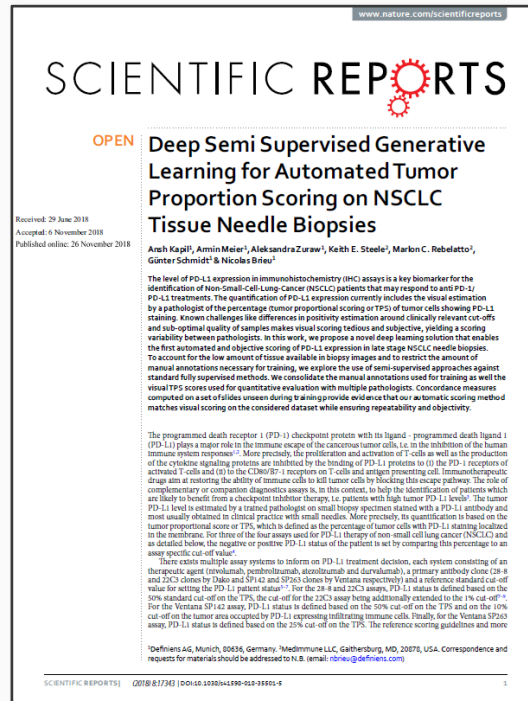8) Image source CAP Today: http://captodayonline.com/scoring-gastric-gej-cancers-pd-l1-expression/

Image analysis-enabled comparisons of 4 PD-L1 assays

▶ Comparison study across 4 existing PD-L1 assays conducted with MedImmune (ESMO 2017)

▶ Findings consistent with blueprint study

▶ Demonstrates technical feasibility of relating PD-L1 scores across assays quantitatively with image analysis
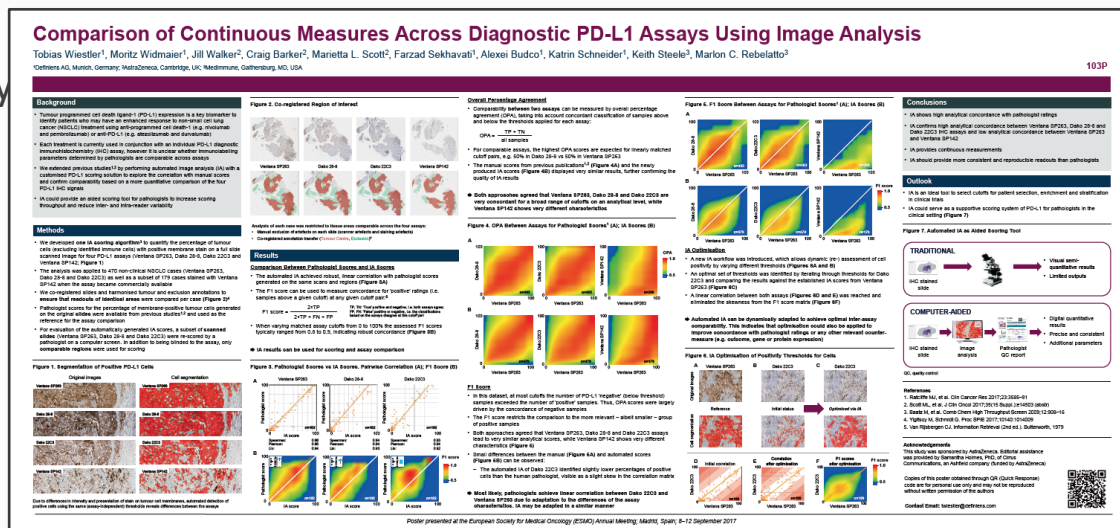
# Deep learning-based solution as good a human pathologists

- Peer-reviewed article published by Definiens & MedImmune

- Deep learning model is as good a a human patholologist in PD-L1 scoring

- Applicable for both resections and biopsies in NSCLC

SCIENTIFIC REPORTS

OPEN **Deep Semi Supervised Generative Learning for Automated Tumor Proportion Scoring on NSCLC Tissue Needle Biopsies**

AC-GAN — Neg (n=86) — Pos (n=67)

Med. Path. - - Neg (n<=80) - - Pos (n=73)

This translates into the stratification of monotherapy Durvalumab-treated NSCLC patients (SITC 2018)

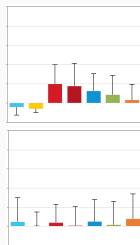# Harmonized tissue Immuno-profiling based on multiplex IHC
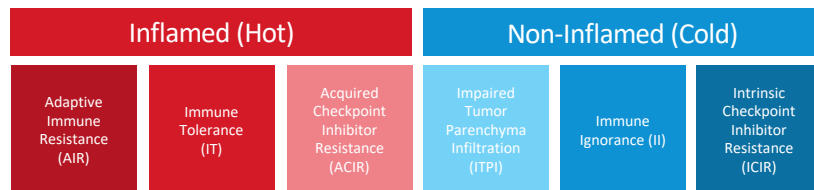
1. Quantification of IHC multiplexes
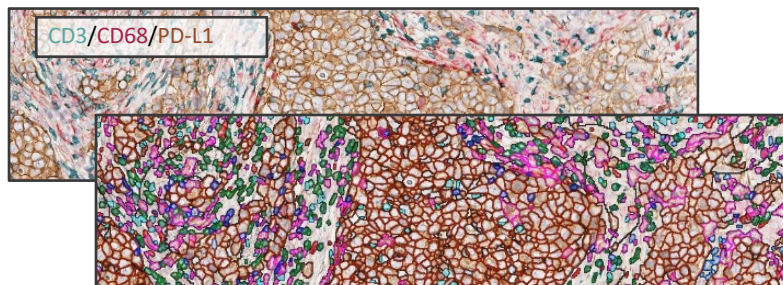
CD3/CD68/PD-L1

Slide Images: Courtesy Mosaic Laboratories Inc., Lake Forest, CA
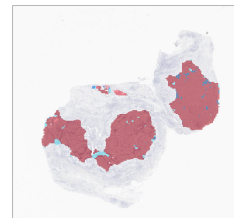
2. Spatial patterns within tissue patches

- CD68
- PD-L1
- CD3
- CD8
- FoxP3
- Granz B
- PD-1

IT

ITPI

3. IO profile per case & assessment of tumor heterogeneity

Inflamed (Hot)			Non-Inflamed (Cold)		
Adaptive Immune Resistance (AIR)	Immune Tolerance (IT)	Acquired Checkpoint Inhibitor Resistance (ACIR)	Impaired Tumor Parenchyma Infiltration (ITPI)	Immune Ignorance (II)	Intrinsic Checkpoint Inhibitor Resistance (ICIR)

AIR **IT** **ITPI**

4. Scale to consistenly profiled cases

RUO, categories are based on scientific research
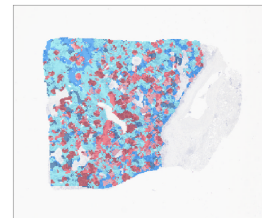
Fully automated immune profiling
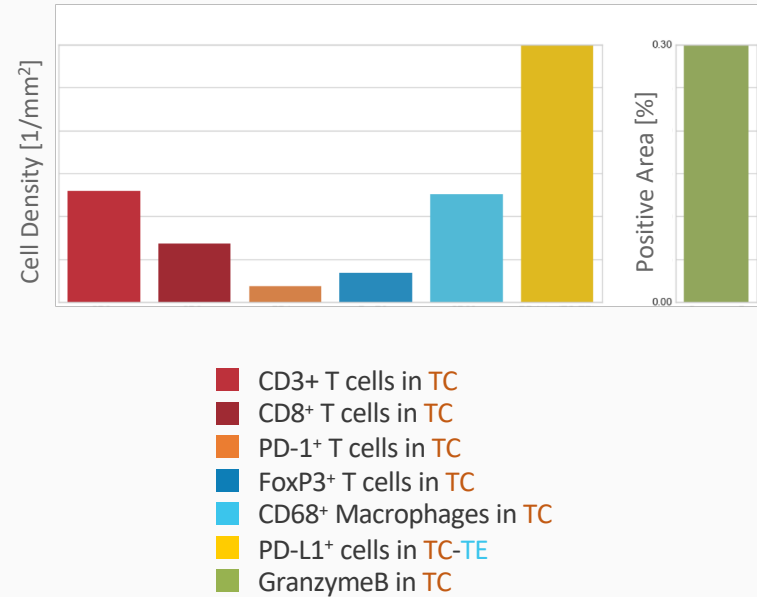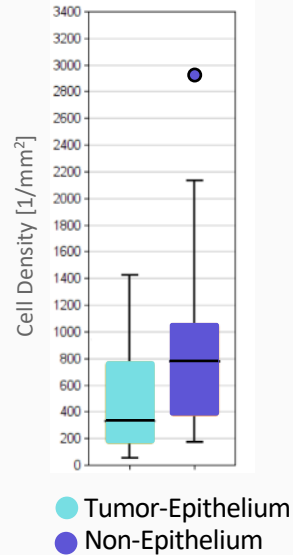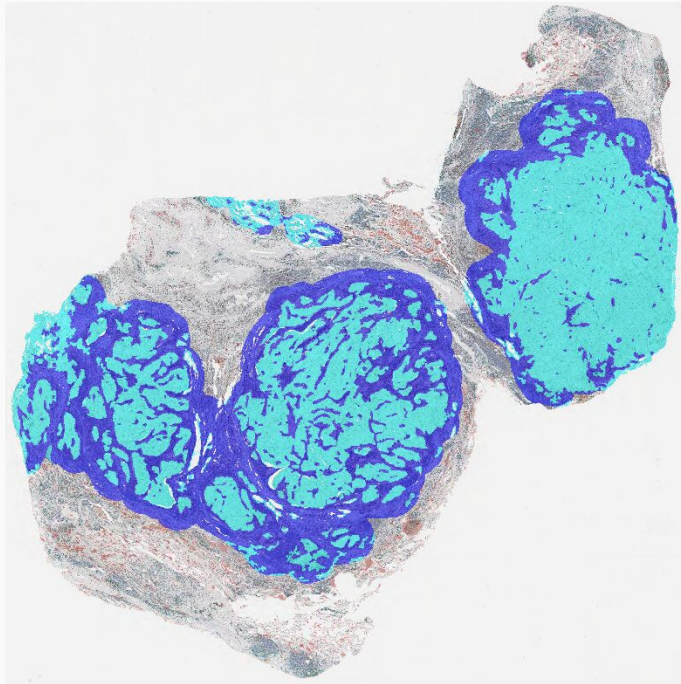
Slide Images: Courtesy Mosaic Laboratories Inc., Lake Forest,
Image Analysis Definiens AG

- Tumor-Epithelium
- Non-Epithelium

- CD3+ T cells in TC
- CD8+ T cells in TC
- PD-1+ T cells in TC
- FoxP3+ T cells in TC
- CD68+ Macrophages in TC
- PD-L1+ cells in TC-TE
- GranzymeB in TC

Spatial characterization of a patient's tumor immune status

A Big Data Approach to Tumor and Patient Classification

Our People & Tools

Bioinformaticians, biostatisticians, translational scientists, clinical and regulatory experts
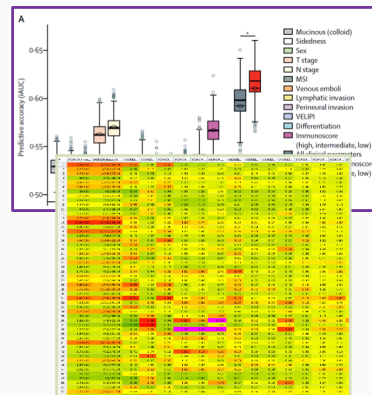
- ▶ Data Mining
- ▶ Machine Learning
- ▶ Bioinformatics
- ▶ Biostatistics

Biomarker Clustering
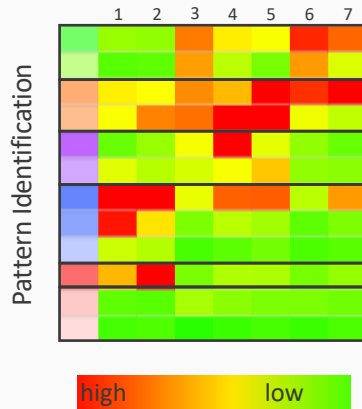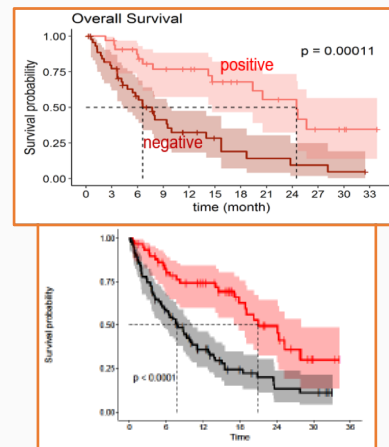

Hypothesis validation and generation

Multi-omic Integration

Genomics, transcriptomics, radiomics

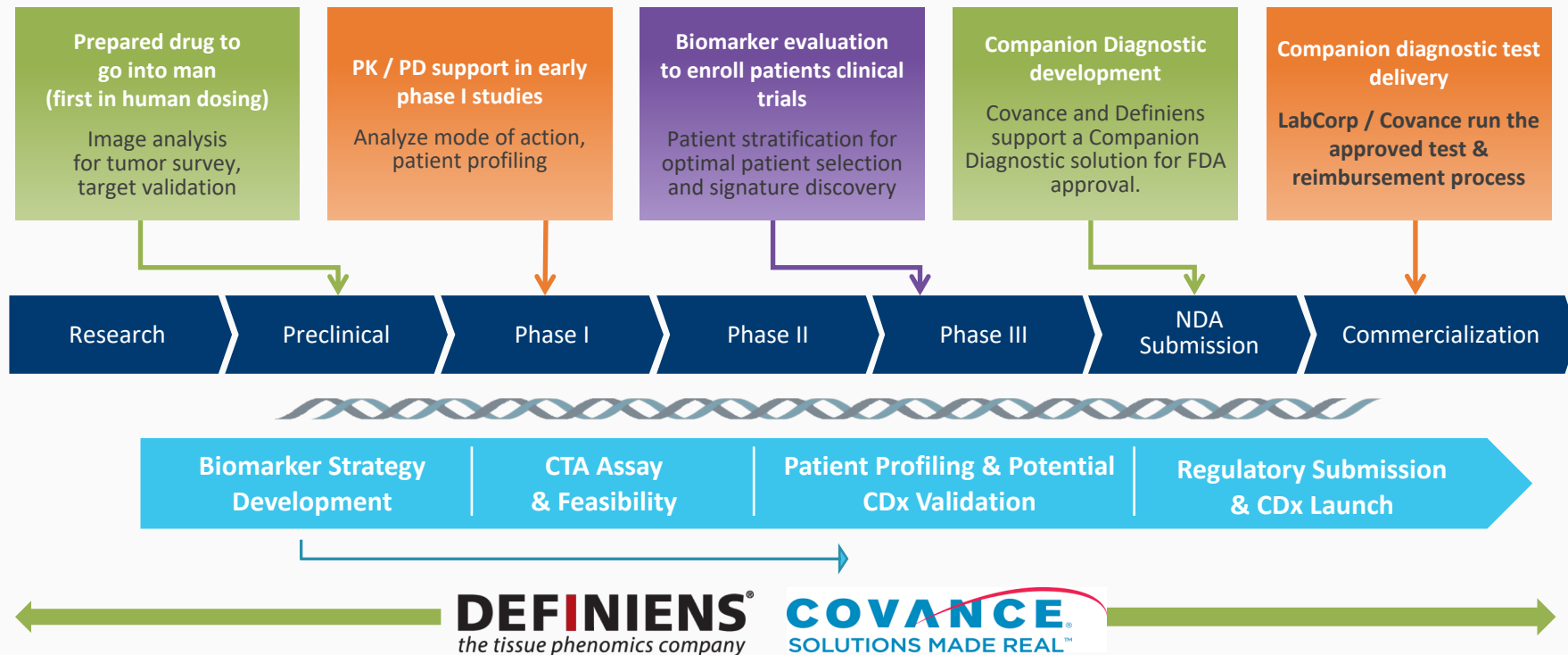## Patient Stratification

More precise patient selection

Enhanced Biomarker and CDx Capabilities in a partnership model

Delivering Comprehensive Biomarker Strategies

At every phase of drug development lifecycle

Prepared drug to go into man (first in human dosing)

Image analysis for tumor survey, target validation

PK / PD support in early phase I studies

Analyze mode of action, patient profiling

Biomarker evaluation to enroll patients clinical trials

Patient stratification for optimal patient selection and signature discovery

Companion Diagnostic development

Covance and Definiens support a Companion Diagnostic solution for FDA approval.

Companion diagnostic test delivery

LabCorp / Covance run the approved test & reimbursement process

| Research | Preclinical | Phase I | Phase II | Phase III | NDA Submission | Commercialization |

Biomarker Strategy Development | **CTA Assay & Feasibility** | **Patient Profiling & Potential CDx Validation** | **Regulatory Submission & CDx Launch**

DEFINIENS® the tissue phenomics company

COVANCE SOLUTIONS MADE REAL™

Thank you