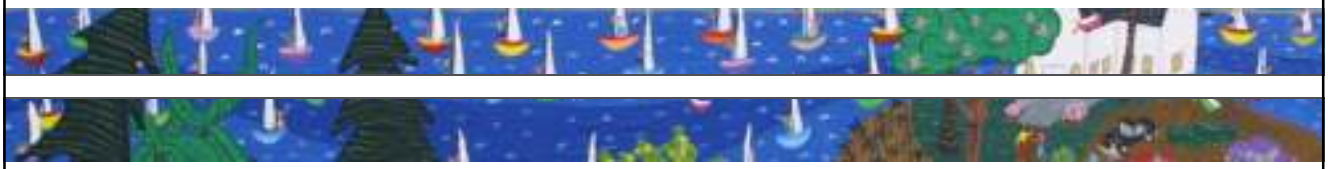
PDL1-Multiple Drugs and Multiple Assays in Development Drug and IVD Company Perspectives



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Janssen Pharmaceuticals

October 8, 2015

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Janssen is proud to feature artwork created by people affected by the illnesses and diseases we are committed to treating and preventing.

OVERVIEW

- Definitions
- History of Immuno-Oncology
- The Case of PD-L1
- Companion Diagnostic Development

US FDA Definition of IVDs

IVDs are a subset of medical devices which are

" . . **reagents, instruments, and systems** intended for use in the **diagnosis of disease or other conditions**, including a determination of the state of health, in order to cure, **mitigate, treat, or prevent disease or its sequelae.**"

Such products are intended for use in the collection, preparation, and examination of specimens taken from the human

(21 CFR 809.3)

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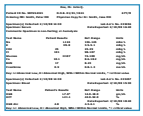
In Vitro Diagnostic (IVD)

IVD: Reagents and systems used for testing specimens taken from the body

Reagents  + Lab Analysis Systems  + Information/Results  = Traditional IVD

Comprised of many unique technology segments

Clinical Chemistry 

Immuno-Assays 

Immuno-Hematology 

Cellular 

Molecular 

Histology/Cytology 

Cytometry 

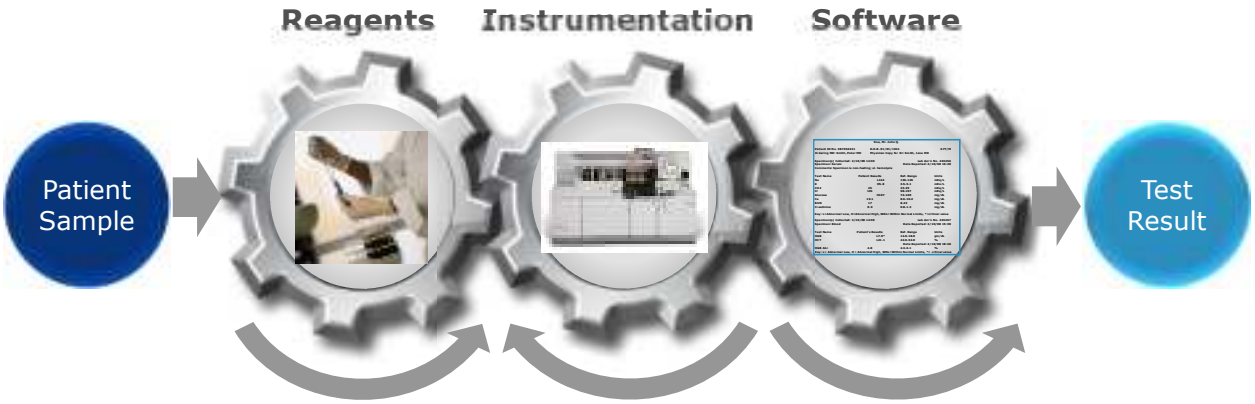
Coagulation 

Microbiology 

Regulatory: What is being Approved?

IVD comprises reagents and systems used for testing specimens taken from the body, typically performed in a lab

FDA reviews 3 components of the test and their interactions



Companion Diagnostic

- "An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product." *

- In most circumstances (new drug or new indication), an IVD companion diagnostic device and its corresponding therapeutic product should be **approved or cleared contemporaneously** for the use indicated in the therapeutic product labeling.

**FDA definition.*

Current Companion Diagnostic Examples

Many successful companion diagnostic/therapeutic co-approvals
– www.fda.gov/companiondiagnostics

CoDx Complexities - Easy Cases:

- One drug, one disease indication, one test, one allele:
  e.g., Abbott VYSIS ALK Break Apart FISH Probe Kit for Xalkori ® (crizotinib)
- One test, one indication, more than one drug, same alleles
  - E.g., QIAGEN *therascreen* KRAS RGQ PCR Kit– for CRC for two therapeutics Erbitux® (cetuximab) and Vectibix® (panitumumab).
- Originally one drug, one indication:
  - HER2 and Herceptin –breast cancer (Tests - Dako IHC / Vysis PathVysion FISH)
  - Follow on tests demonstrated method comparison, development of CAP guidelines
  - Expanded the indication to gastric cancer
  - Other drugs for the same analyte - Perjeta, Kadcyla

U.S. Food and Drug Administration
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CoDx Complexities

One indication, More than one drug, Two tests- Same gene but different allele representation.

- BRAFV600 mutation:
  - Roche cobas BRAF V600 Mutations Test for Zelboraf® (vemurafenib)
  - BioMérieux THxID BRAF Kit for Tafinlar® (dabrafenib) and Mekinist® (trametinib)
- EGFR Activating Mutations
  - Roche cobas EGFR Mutation Test for Tarceva® (erlotinib)
  - Qiagen *therascreen* EGFR RGQ PCR Kit for Gilotrif® (afatinib)

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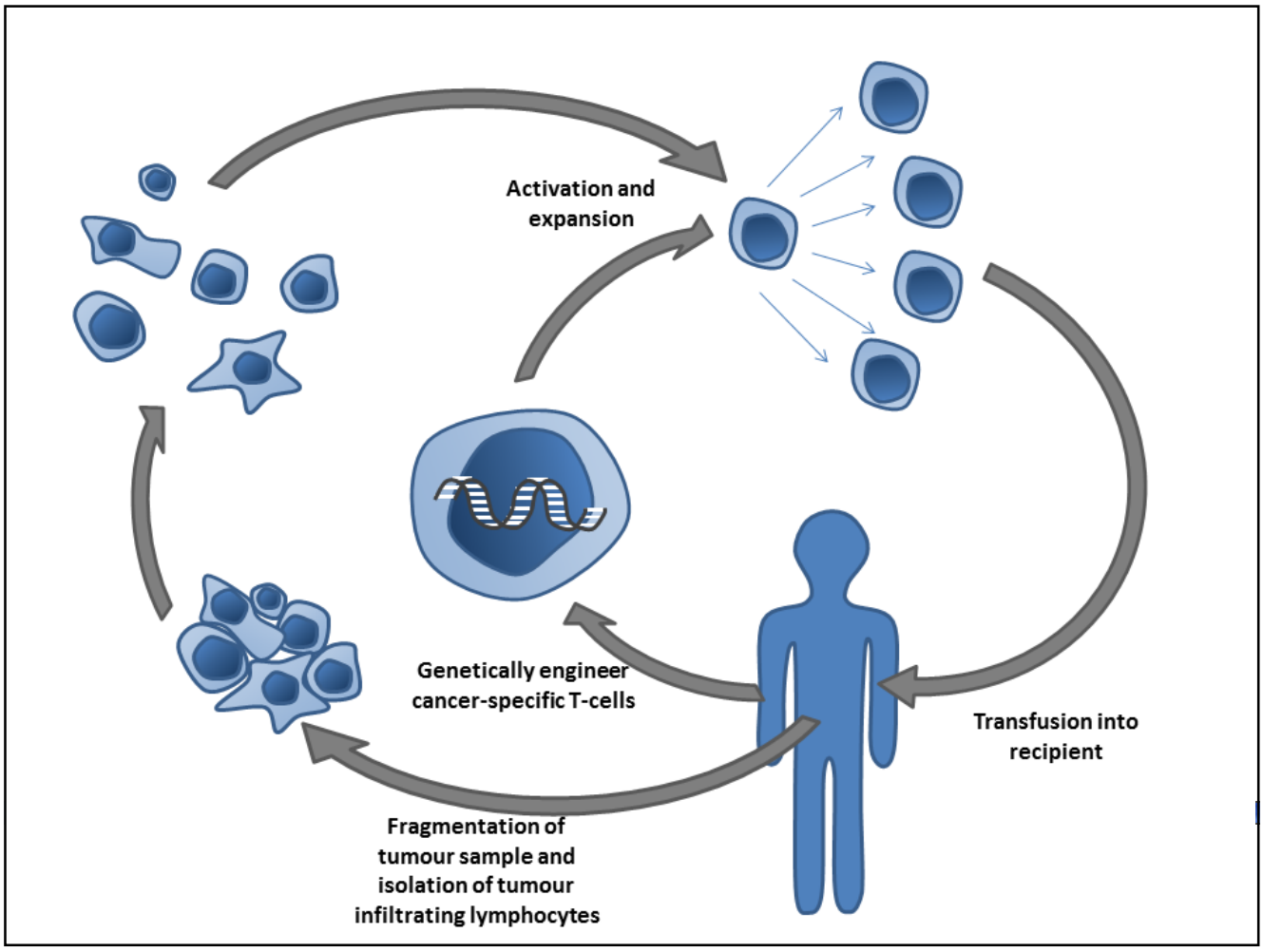
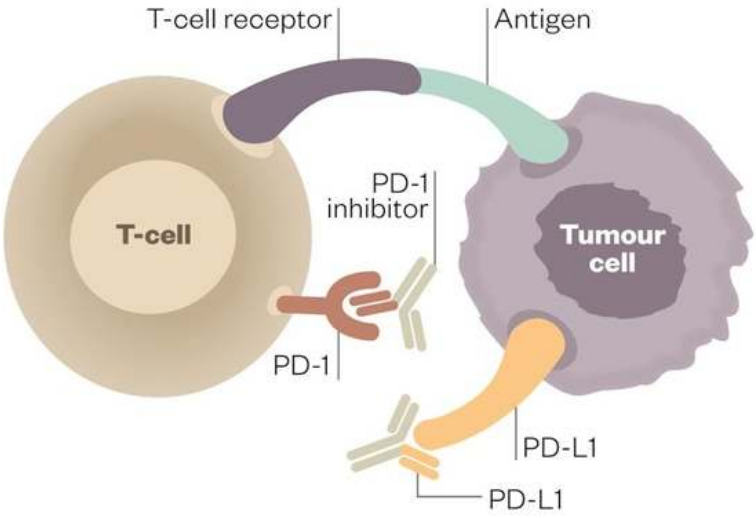
Cancer immunotherapy (**immuno-oncology**) is the use of the immune system to treat cancer.

The immune system is the body's natural defense system.

- Cancer cells can be very different(foreign) from normal cells do the immune system attacks them.
- Cancer cells often find ways to disguise themselves as normal cells or, similar to viruses, cancer cells can change over time (mutate) and therefore escape from the immune response.
- Natural immune response to cancer cells is often not strong enough to fight off cancer cells.
- Immuno-oncology works by activating our immune system to recognize cancer cells and destroy them.


Activation and expansion
Genetically engineer cancer-specific T-cells
Transfusion into recipient
Fragmentation of tumour sample and isolation of tumour infiltrating lymphocytes


T-cell receptor
Antigen
PD-1
inhibitor
T-cell
Tumour
cell
PD-1
PD-L1
PD-L1

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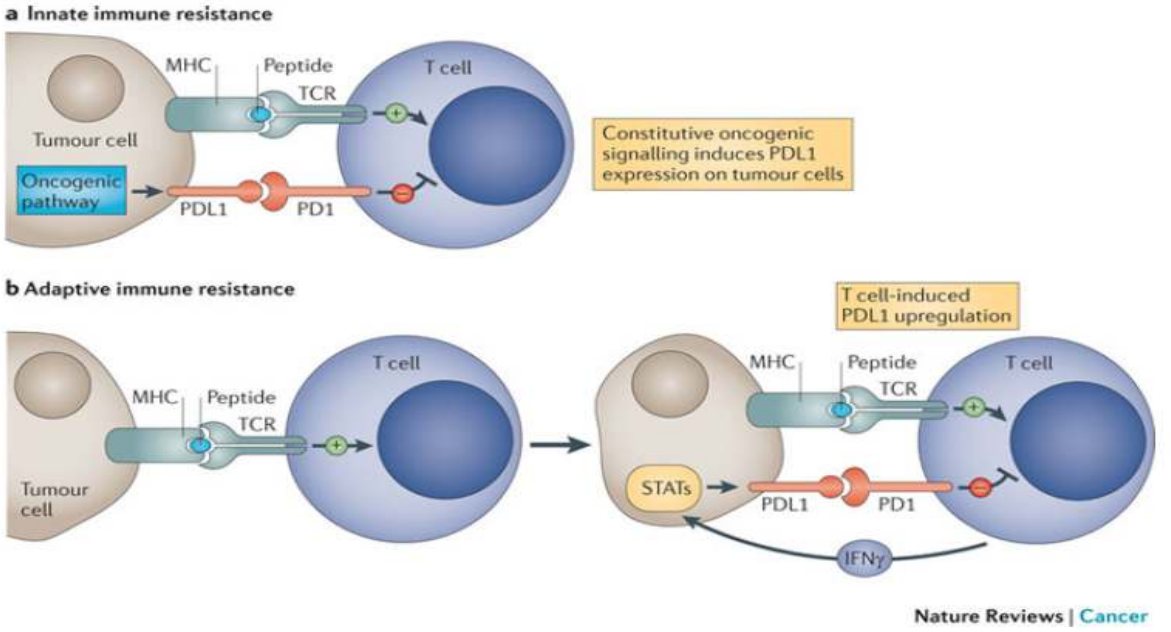
The Case of PD-L1



Nature Reviews | Cancer

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PD-L1 IHC Methods in Development

	Hopkins	BMS	Merck	Genentech
mAb clone	5H1	28-8	22C3	SP142
Automated	No	Yes	Yes	Yes
Staining location scored	Membrane	Membrane	Membrane	Membrane
Cell type(s) scored	Tumor cells	Tumor cells	Tumor and/or infiltrating immune cells	Infiltrating immune cells
Positive cutoff	≥ 5%	≥ 5%	≥ 1%	≥1% to ≥10% ("IHC 1-2-3")

Topalian 2015

- ***Note**: These assays are evolving, pending further clinical correlations*

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PD-1 Blocking Antibodies

- **Nivolumab** (**ONO-4538**, **BMS-936558**, or **MDX1106**), developed by Ono Pharmaceutica and Medarex (Medarex was later acquired by **Bristol-Myers Squibb**) and marketed as **Opdivo**, is a fully humanized IgG4 monoclonal antibody that blocks PD-1
- **Pembrolizumab** (formerly **MK-3475** and **lambrolizumab**, trade name **Keytruda; Merck**) is a humanized monoclonal IgG-4κ antibody that blocks PD-1

Anti-PD-L1 Antibodies

- **MPDL3280A (Roche)** is a humanized IgG-1κ monoclonal anti-PD-L1 antibody. It is genetically engineered to modify the Fc domain, thereby impairing the antibody-dependent cellular cytotoxicity of PD-L1 expressing cells
- **MEDI4736 (AstraZeneca)** is a humanized IgG-1κ monoclonal antibody that blocks PD-L1

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Nivolumab (Opdivo/BMS)

- **FDA approval:** Treated Squamous cell non–small cell lung cancer (NSCLC) that has progressed based on CheckMate-017, A Phase III study of Nivolumab vs Docetaxel in 2nd Line Squamous Cell. *Responses were observed independent of PD-L1 status*

- "Importantly, PD-LI emerged as a clear predictive factor for the benefit of nivolumab," Dr. Paz-Ares stated at the ASCO 2015 press conference

- Recent: Checkmate 057, a Phase III, open-label, randomized study of Nivolumab versus docetaxel in previously treated patients with advanced or metastatic non-squamous NSCLC

Pembrolizumab (Keytruda/Merck)

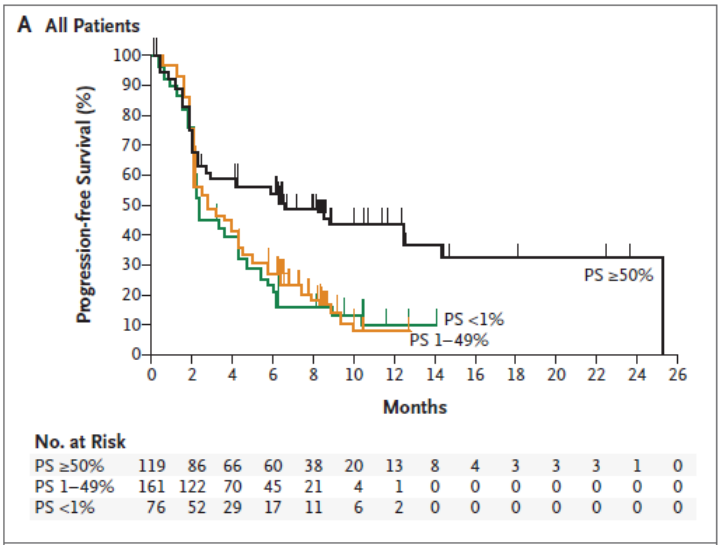

Figure 3. Progression-free Survival.

Shown are Kaplan–Meier estimates of progression-free survival according to the proportion score (PS) — the percentage of neoplastic cells with membranous PD-L1 staining — for 356 patients in the training and validation groups who had slides that were sectioned within 6 months before staining (Panel A), including 294 previously treated patients (Panel B) and 62 previously untreated patients (Panel C).

"These data in combination with responses among patients with a proportion score of less than 1% suggest that tumor PD-L1 expression is not associated with the ideal test characteristics of approved genetically based biomarkers. It is likely that tumor PD-L1 expression alone does not accurately assess the "dynamic immune microenvironment."

Garon et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer NEJM 2015

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MPDL3280A (Roche)

- FDA breakthrough designation: treatment of patients with PD-L1–positive non–small cell lung cancer (NSCLC) that has progressed during or after platinum-based chemotherapy, as well as a targeted therapy for patients with EGFR- or ALK-positive tumors. (Phase I study; PDL1 as inclusion criterium)

- Ongoing: -A Phase 2 Study of MPDL3280A Compared With Docetaxel in Patients With Locally Advanced or Metastatic NSCLC Who Have Failed Platinum Therapy "POPLAR". Interim results: MPDL3280A reduced the risk of death by 53% ([OS]; [HR]=0.47) in people whose cancer expressed the highest levels of PD-L1 compared with docetaxel. An improvement in OS was also observed in people who had medium and high (HR=0.56) or any level of PD-L1 expression (HR=0.63), as characterized by a test being developed by Roche.

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MPDL3280A (Roche)

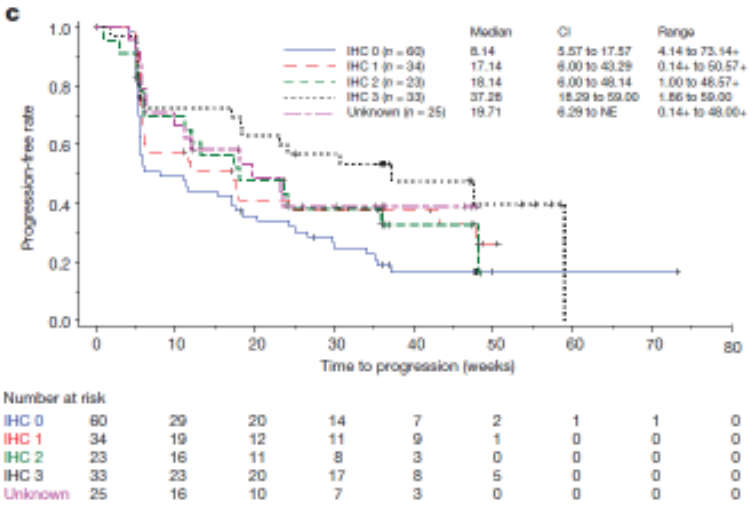

Figure 3 | Antitumour activity of MPDL3280A by immunohistochemistry (IHC) tumour-infiltrating immune cell (IC) and biomarker status. a, Table

The association of response to MPDL3280A treatment and tumour-infiltrating immune cell PD-L1 expression reached statistical significance (NSCLC, P=0.015),while the association with tumour cell PD-L1 expression did not (NSCLC, P=0.920)

Herbst et al "Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients" Nat Let 2015

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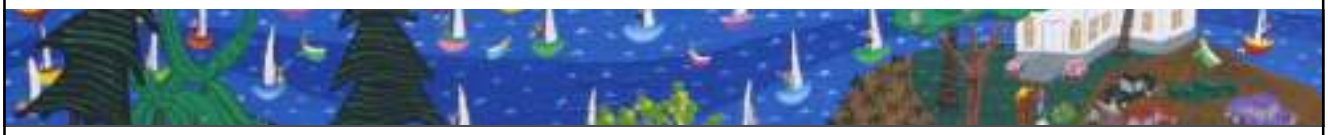
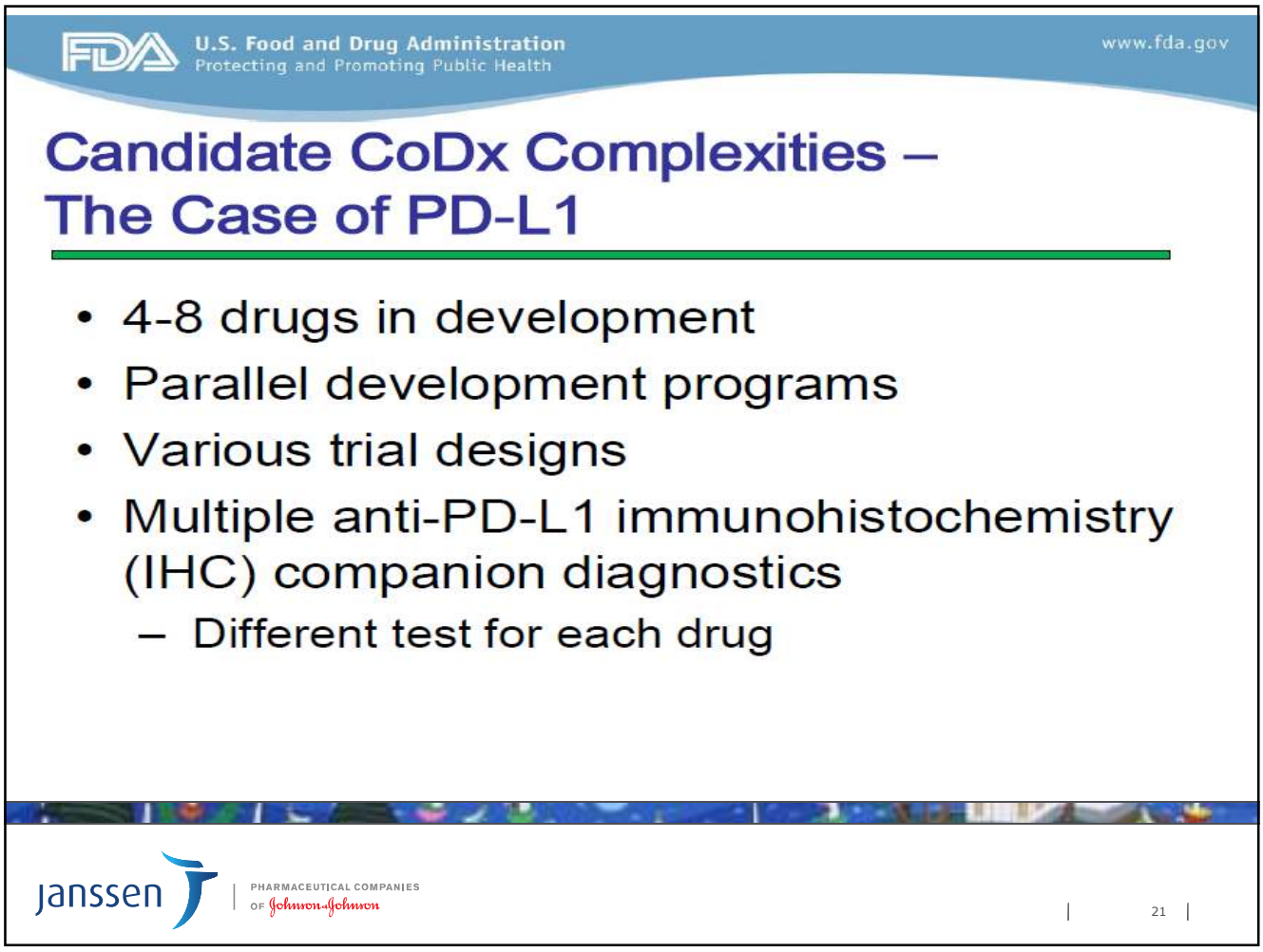
Problematic for the following reasons

- High potential for mismatched approved drug/device combination in the clinical setting. Patient treatment may not be based on testing with the matched CoDx.
- FDA approvals are for a specific drug/CoDx combination, so the labeling applies only to that particular combination. Performance across different clinical decision points (cut-offs) may not be established.
- Laboratories are not able to assess the impact of discordance between tests in the absence of clinical outcome data.
- Laboratories are not expected to have more than one assay/platform to detect the same analyte.

THANK YOU!

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Candidate CoDx Complexities – The Case of PD-L1
• 4-8 drugs in development
• Parallel development programs
• Various trial designs
• Multiple anti-PD-L1 immunohistochemistry (IHC) companion diagnostics
– Different test for each drug
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