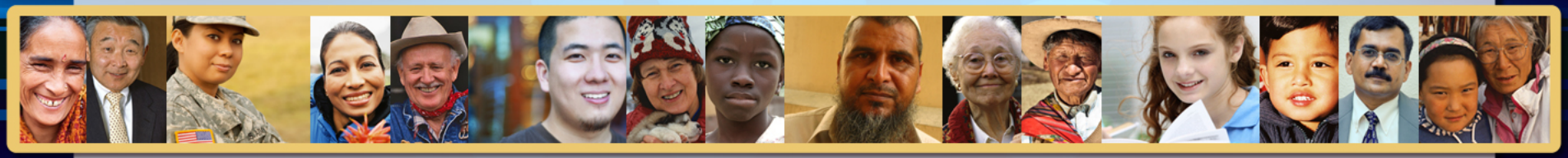
NAS Enabling Precision Medicine
Session III Reaction
March 8, 2017

Economics, Genetics and Clinical Development



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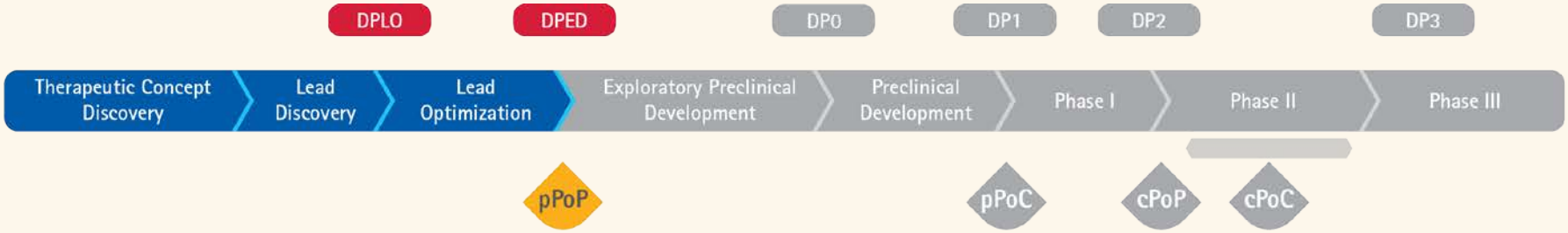
Successful Clinical Development Requires Extensive Preclinical Effort

Genetics Driven development must begin as early as Exploratory Development (Merck/EMD Serono experience)



Target	Dose & Drug	Patient
Is the preclinical Proof of Principle (pPoP) established with the proposed pre-candidate drug(s)? Are relevant safety species identified based on target expression, metabolite pattern, drug exposure and immunogenicity? Are "fit for purpose" biomarker assays available for preclinical models and safety species? Which assays are translatable for clinical use?	Has at least one pre-candidate drug been identified with the desired exposure-response relationship and translatable pharmacodynamic biomarker(s)? What is the expected therapeutic window based on preliminary non-clinical safety data (e.g., *in vitro* selectivity, limited *in vivo* toxicology study)?	What efficacy and benefit/risk can be anticipated based on the Merck Serono-generated evidence with the pre-candidate drugs? **Is the range of target and pathway variability in the intended indication(s) potentially suitable for a stratified medicine approach? Is this information incorporated into the biomarker and early clinical strategy?**

Dolgos H, Tusheim MR, et al. "Translational medicine guide transforms drug development processes: the recent Merck experience." *Drug discovery today* 21.3 (2016): 517-526.

Biomarker and Companion Diagnostic Strategy Must Evolve Systematically Throughout Early Development

Developing evidence to address critical science questions and capabilities is proving a key to success

	DPLO	DPED	DP0	DP1	DP2	cPoC
Target	Is a biomarker strategy established?	Are "fit for purpose" biomarker assays available for preclinical models and safety species? Which assays are translatable for clinical use?		Are translatable pharmacodynamic biomarkers measurable in the Phase I population through analytically validated methods?		
Dose & Drug		Has at least one pre-candidate drug been identified with the desired exposure-response relationship with translatable pharmacodynamic biomarker(s)?				
Patient		Is the range of target and pathway variability in the intended indication(s) potentially suitable for a stratified medicine approach? Is this information incorporated into the biomarker and early clinical strategy?	What is the preliminary clinical development strategy (as supported by the biomarker strategy), including the outline for first in human trial(s)?	What is the design of the initial clinical trials, as supported by the biomarker strategy? What is the evidence to support population selection for the Phase I program? Are there analytically or clinically validated methods already available enabling patient stratification? What is the anticipated distribution (variance) of the candidate stratification biomarker in the intended population?	If a stratification biomarker will be deployed for efficacy (or safety), which analytically or clinically accepted methods are proposed? Is a companion diagnostic development strategy included?	

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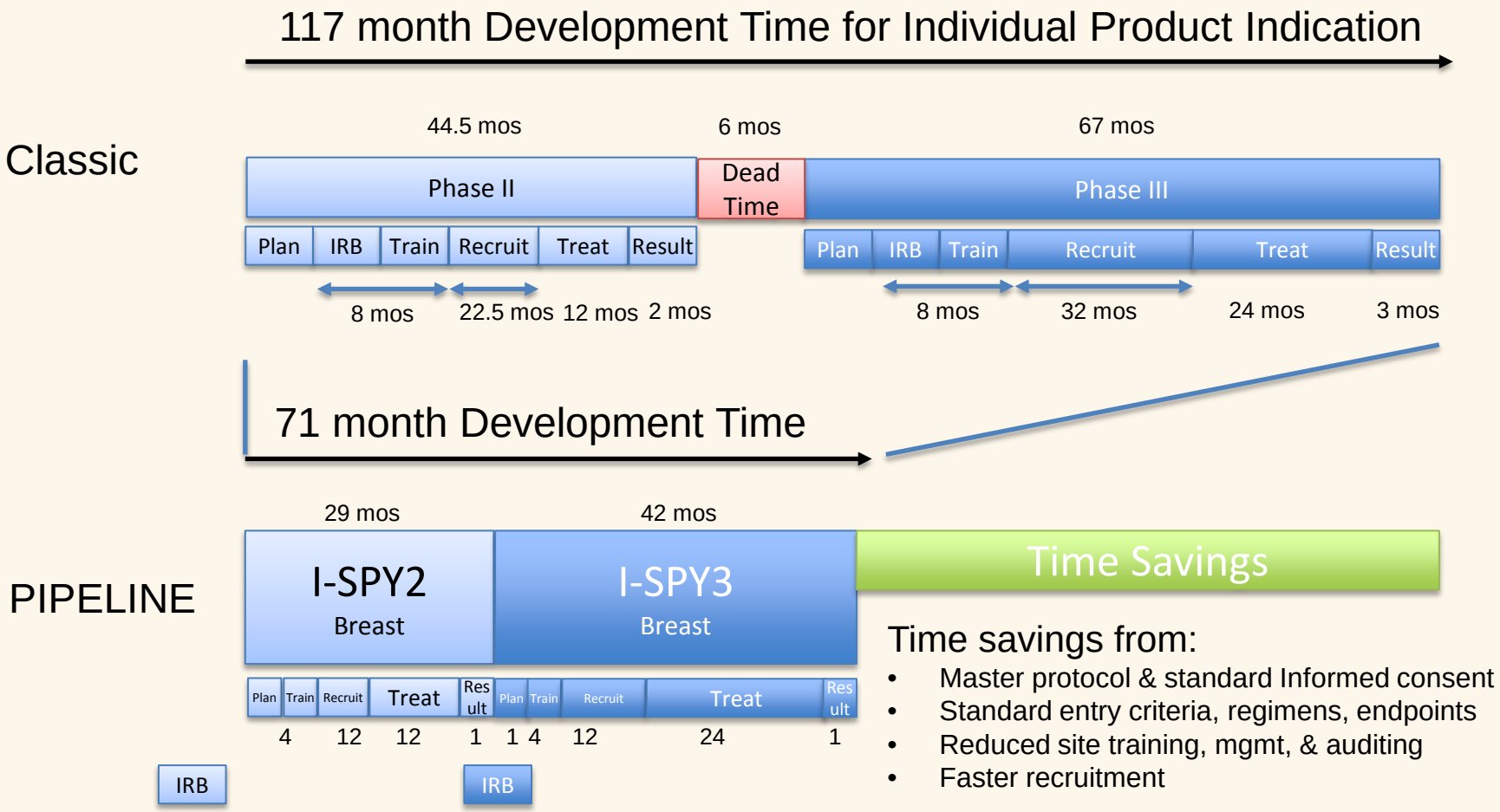
Genetics Driven Development Requires Economies of Scale that Linked Platform Trials (PIPELINEs) Can Deliver



Time savings from:

- Master protocol & standard Informed consent
- Standard entry criteria, regimens, endpoints
- Reduced site training, mgmt, & auditing
- Faster recruitment

(Modified from Trusheim et al, PIPELINES/CP&T December 2016)