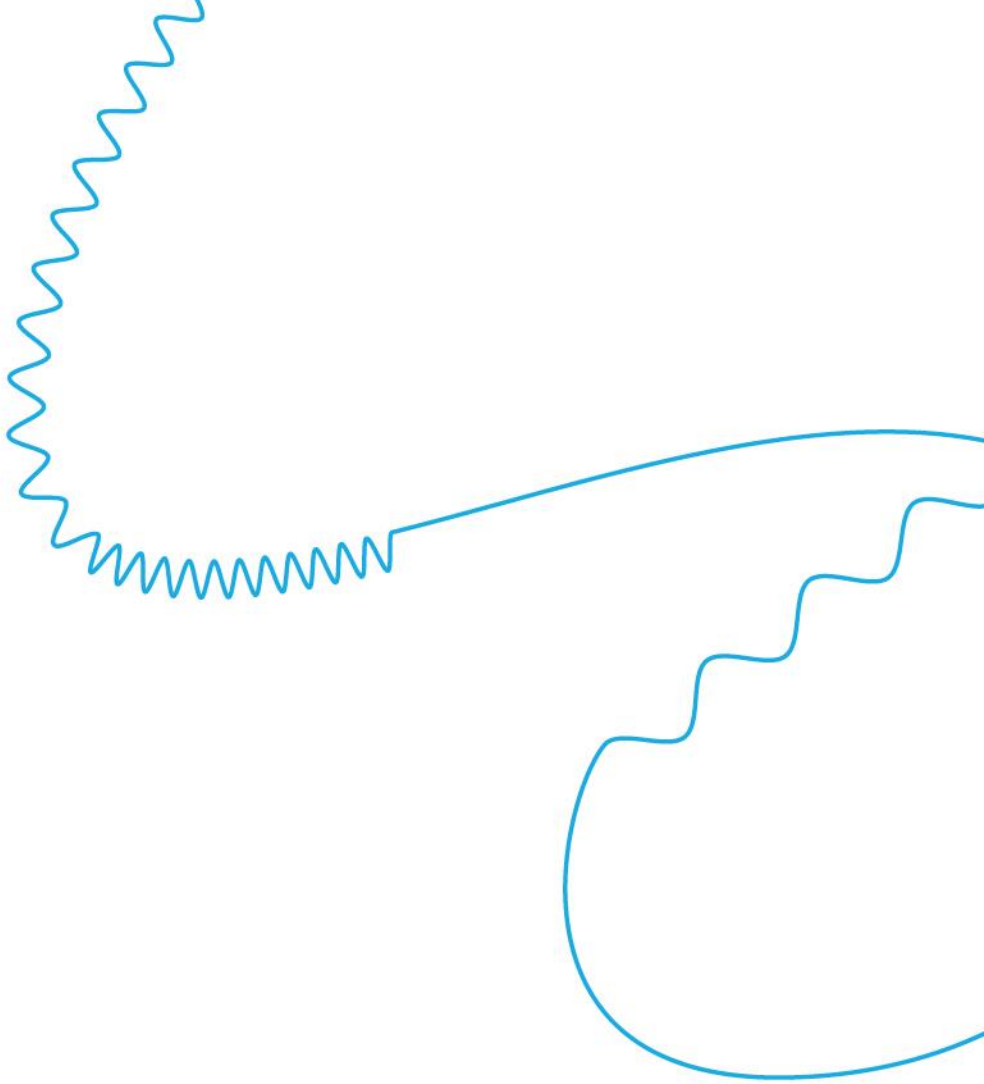
Annual R&D Day

September 8th, 2022



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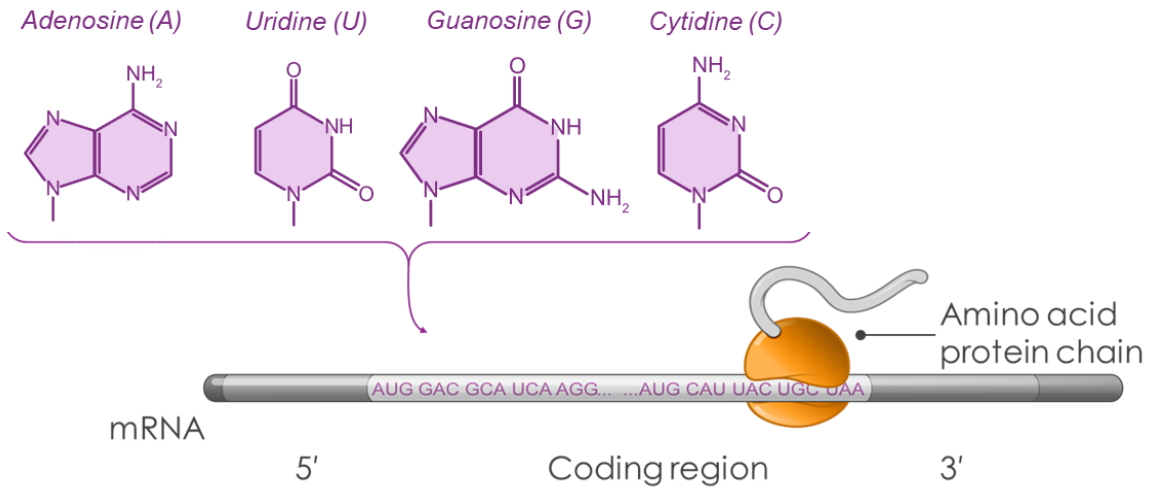
Forward-looking statements and disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including statements regarding: Moderna's vision for mRNA science; the timing of data from Moderna's trials of its product candidates targeting PCV, MMA, GSD1a and RSV; clinical trends in Moderna's Phase 1/2 PA trial; Moderna's launch of COVID-19 vaccine boosters; the initiation of clinical trials for mRNA-1230, targeting SARS-CoV-2, influenza and RSV; Moderna's pursuit of an accelerated approval pathway for mRNA-1010; expected read out of Moderna's Phase 3 immunogenicity trial of mRNA-1010; expected initiation of Moderna's Phase 3 efficacy study of mRNA-1010; enrollment in Moderna's Phase 3 trial of its CMV vaccine candidate; Moderna's commercial organization strategic priorities; the timing of potential future product launches; Moderna's transition to an endemic COVID market; the respiratory vaccines market opportunity, including for COVID-19 vaccines, and the potential to expand the market; the market potential of adult combination vaccines; the market opportunity for vaccines for latent viruses; the market opportunity for therapeutics for rare diseases; and Moderna's manufacturing capabilities. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "could," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others, those risks and uncertainties described under the heading "Risk Factors" in Moderna's Annual Report on Form 10-K for the year ended December 31, 2021 and Quarterly Report on Form 10-Q for the quarter ended March 31, 2022, each filed with the U.S. Securities and Exchange Commission (SEC), and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date of this presentation.

mRNA is the software of life

Binary System

Quaternary System



mRNA is an information molecule

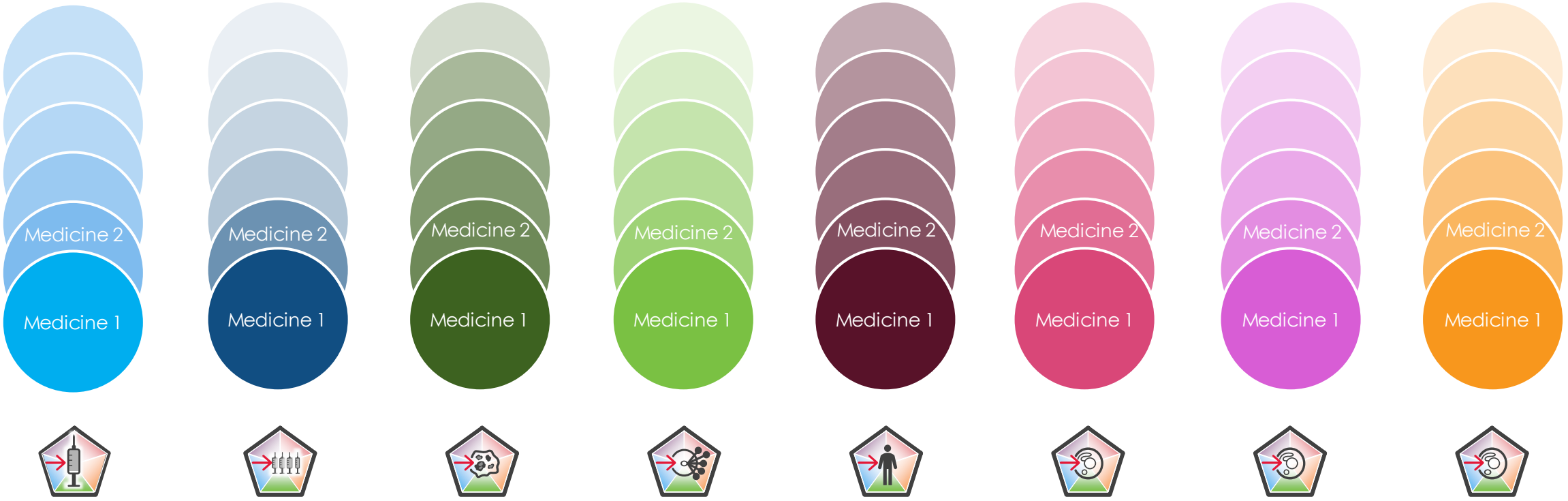
Moderna's vision for mRNA science

1

mRNA is an information molecule

2

Invest in science to invent novel ways to deliver mRNA into various cell types – each will be a new application, which we call a modality



Proof-of-concept data from our sentinel programs de-risk our modalities and accelerate our development plans

EXPLORATORY — EMERGING — ESTABLISHED

Modalities	Inhaled pulmonary therapeutics	Localized regenerative therapeutics	Intratumoral immuno-oncology	Cancer vaccines	Systemic secreted & cell surface therapeutics	Systemic intracellular therapeutics	Prophylactic vaccines: *Latent virus vaccines*	Prophylactic vaccines: *Respiratory vaccines*
Sentinel programs	CF	VEGF-A (no LNP)	Triplet	Personalized cancer vaccine	Chikungunya antibody	PA	CMV vaccine	COVID-19 vaccine

- Six programs; four in clinical trials

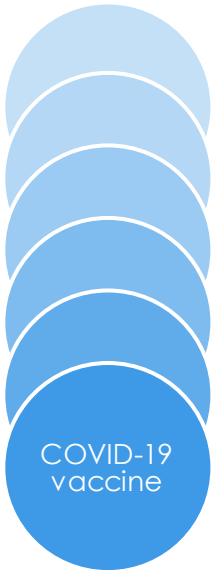
- Chikungunya antibody data in 2019 de-risked systemic LNP delivery
- Emerging data from PA suggesting clinical benefit
- Personalized cancer vaccine (PCV) Phase 2 data expected in 4Q22

- Respiratory vaccines de-risked
- Latent virus vaccines efficacy readout to come from CMV

Increasing R&D investment

Proof-of-concept data in vaccines were an enabler

Expansion of vaccines modality



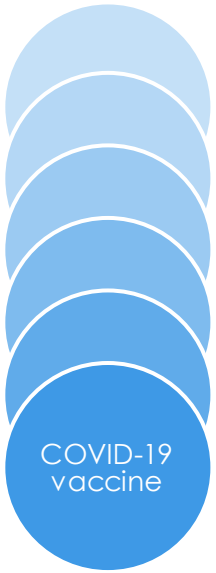
Prophylactic vaccines

Proof-of-concept data achieved in vaccines

- Enabled Moderna to quickly develop a vaccine against COVID-19
- Expanded vaccine pipeline with the addition of new vaccine development candidates
  - R&D Day 2019: 7 vaccine programs
  - R&D Day 2022: 32 vaccine programs

Platform advantages and increased investments accelerated vaccine pipeline development

Expansion of vaccines modality



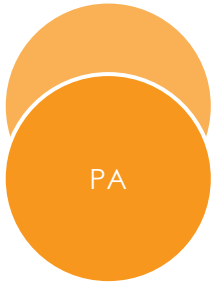
Prophylactic vaccines

Increased investments and execution accelerated the development of vaccines

- **4 vaccines in late-stage, Phase 3 programs**
  - R&D Day 2019: 0 late-stage programs
  - R&D Day 2022: 4 late-stage programs
- **24 vaccines currently in the clinic**
  - R&D Day 2019: 8 vaccines in clinic
  - R&D Day 2022: 24 vaccines in clinic

Early data from our ongoing PA trial is encouraging and shows potential to have a meaningful clinical impact

Systemic intracellular modality



Systemic intracellular therapeutics

Encouraging interim data from PA Phase 1/2 Paramount study

- Generally well-tolerated safety profile to date
- Encouraging data shows decrease in the number of metabolic decompensation events (MDEs)
- Initial discussions with regulators supportive of MDE as primary endpoint for a pivotal study

Encouraging signs in a second rare disease

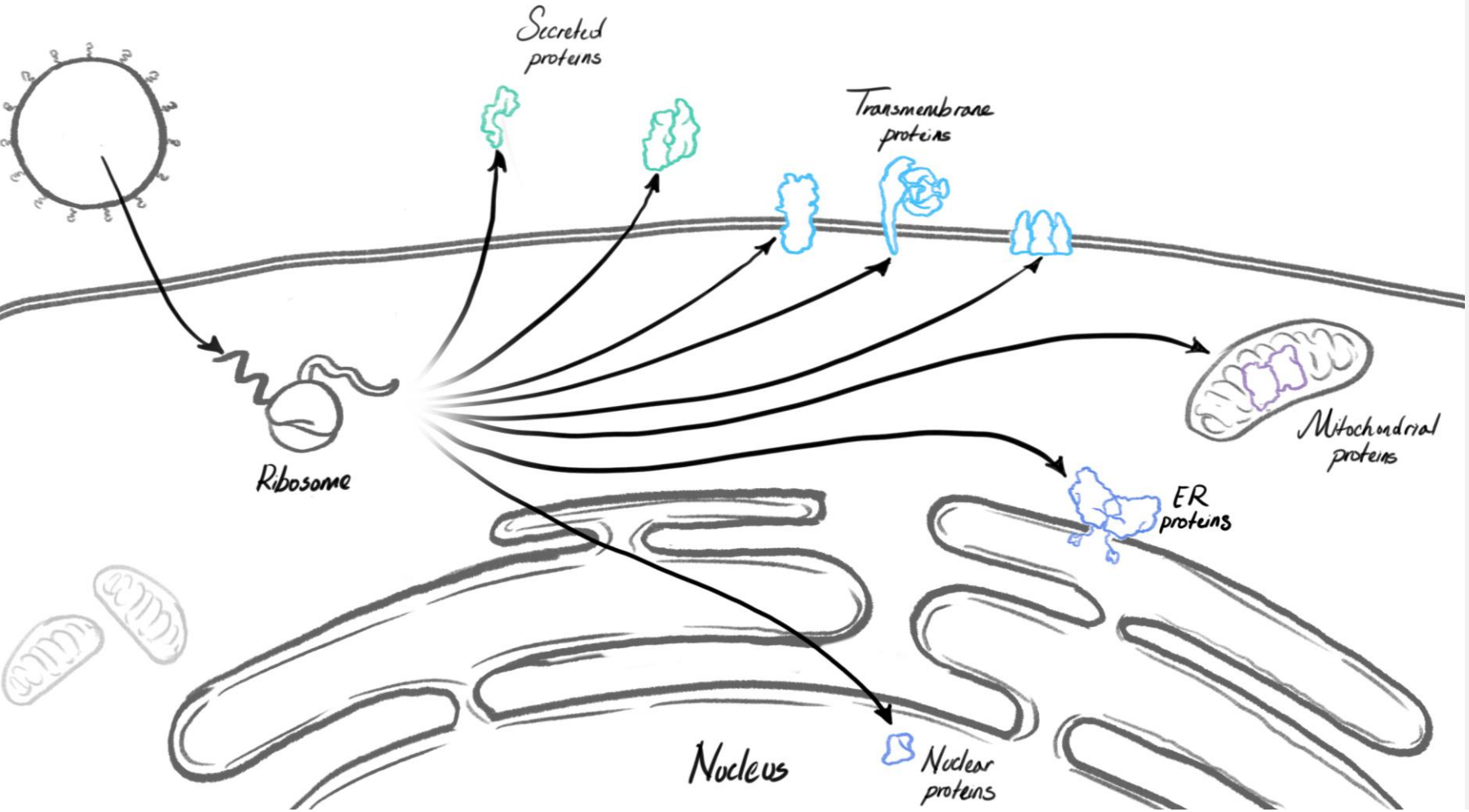
Systemic intracellular modality

Systemic intracellular therapeutics

Encouraging interim data from GSD1a Phase 1/2 Ba1ance study

- Early data on safety and pharmacodynamics are consistent and encouraging
- Announcing new rare disease candidate: Ornithine transcarbamylase deficiency (OTC)
  - OTC is a rare genetic condition that causes ammonia to build up in the blood
  - OTC (mRNA-3139) uses the same LNP as GSD1a program

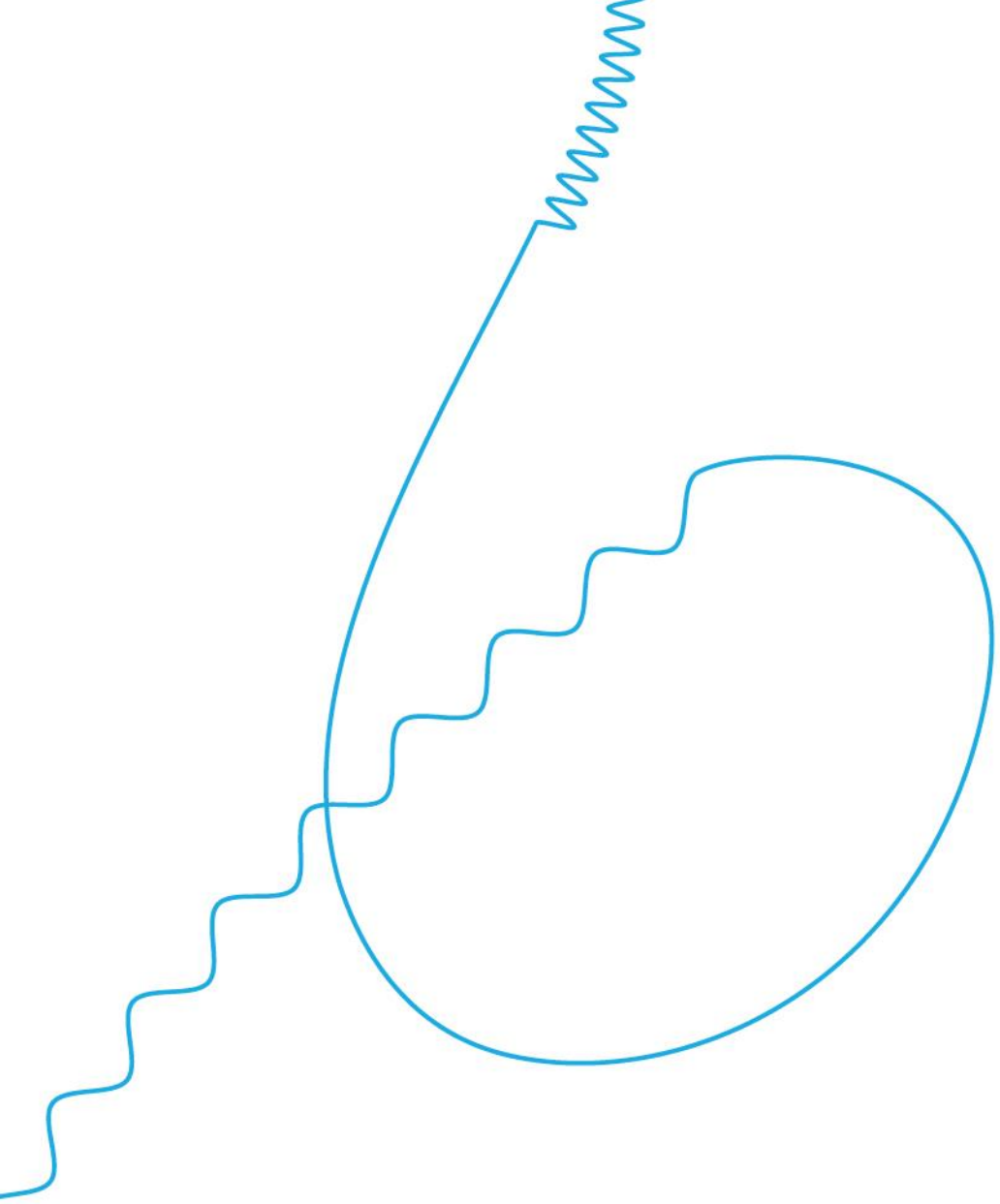
mRNA is a new class of medicines



- COVID vaccines and boosters established mRNA technology for respiratory vaccines
- Respiratory vaccines in Phase 3: seasonal flu, RSV data readouts and launches are next
- We now have encouraging data from our first mRNA therapeutic encoding for an intracellular protein for a rare disease of the liver
- On track to readout PCV Phase 2 data in 4Q22

Today's agenda

Introduction	**Stéphane Bancel**, *Chief Executive Officer*
R&D Day 2022 Overview	**Stephen Hoge, M.D.**, *President*
mRNA Therapeutics	
Rare Diseases • Organic acidemias overview and real-world burden of disease • Interim PA Phase 1/2 data • Interim GSD1a Phase 1/2 data	**Dr. Mark S. Korson,** *Director of Physician Support Service and Education, VMP Genetics* **Ruchira Glaser, M.D.**, *SVP, Head, Therapeutics (Rare Disease, Autoimmune & Emerging)* **Geoffrey Rezvani, M.D.,** *Executive Director, Program Leader (Cardiovascular and Emerging Therapeutics)*
Immune Oncology • Personalized Cancer Vaccine (Phase 2 trial overview)	**Michelle Brown, M.D., Ph.D.,** *Executive Director, Program Leader, Oncology*
Coffee Break (10 minutes)	
Vaccines: Late-Stage Phase 3 Trials	
COVID Booster/Combination Respiratory Vaccines	**Jacqueline Miller, M.D.**, *SVP, Therapeutic Area Head, Infectious Diseases*
Seasonal Influenza Vaccine Phase 3 Trials	**Raffael Nachbagauer, M.D., Ph.D.,** *Senior Director, Infectious Disease Development*
Respiratory Syncytial Virus (RSV) Phase 3 Trial	**Christine Shaw, Ph.D.,** *VP, Portfolio Head Respiratory Vaccines, Infectious Disease Development*
Cytomegalovirus (CMV) Vaccine Phase 3 Trial	**Jacqueline Miller, M.D.**, *SVP, Therapeutic Area Head, Infectious Diseases*
Commercial Organization Launch Preparation	**Arpa Garay,** *Chief Commercial Officer*
Conclusion	**Stéphane Bancel**, *Chief Executive Officer*
Q&A	**Stéphane Bancel, Stephen Hoge, Arpa Garay, Ruchira Glaser, Jacqueline Miller, Praveen Aanur**



R&D Day Introduction

Stephen Hoge, M.D.

President

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Moderna has a diverse portfolio of vaccine and therapeutic programs in preclinical and clinical development

			Preclinical	Phase 1	Phase 2	Phase 3	Licensed
Respiratory Infectious Diseases	mRNA-1273	SARS-CoV-2					
	mRNA-1345	RSV (older adults)					
	mRNA-1010	Seasonal Flu (HA)					
	mRNA-1283	SARS-CoV-2					
	mRNA-1073	COVID + Flu					
	mRNA-1020/-1030	Seasonal Flu (HA+NA)					
	mRNA-1345	RSV (pediatrics)					
	mRNA-1653	hMPV + PIV3 (pediatrics)					
	mRNA-1011/-1012	Seasonal Flu (HA)					
	mRNA-1230	COVID + Flu + RSV					
	mRNA-1287	HCoV					
	mRNA-1365	RSV + hMPV (pediatrics)					
Latent and Public Health Infectious Diseases	mRNA-1647	CMV					
	mRNA-1893	Zika					
	mRNA-1189	EBV					
	mRNA-1574, 1644	HIV					
	mRNA-1215	Nipah					
	mRNA-1195	EBV Therapeutic					
	mRNA-1468	VZV					
	mRNA-1608	HSV					
Rare Diseases	mRNA-3927	PA					
	mRNA-3705	MMA					
	mRNA-3745	GSD1a					
	mRNA-3692	CFTR (Vertex)					
	mRNA-3351	CN1					
	mRNA-3602	PKU					
	mRNA-3139	OTC					
Oncology	mRNA-4157	PCV (Merck)					
	mRNA-5671	KRAS					
	mRNA-2905	IL-12					
	mRNA-2752	Triplet					
	mRNA-4359	Checkpoint Vaccine					
Autoimmune	mRNA-6981	PD-L1					
Cardiovascular	AZD8601	VEGF-A					
	mRNA-0184	Relaxin					

Today we are focusing on late-stage vaccines and proof-of-concept programs

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Today we are focusing on late-stage vaccines and proof-of-concept programs

mRNA therapeutics review

- **Review of interim PA data** from ongoing Phase 1/2, *multiple-dose* study
- **Review of early data** from first patients in ongoing GSD1a Phase 1/2, *single-dose* study
- **Phase 2 personalized cancer vaccine (PCV) trial overview** (data expected in 4Q22)

Late-stage vaccines

- **Overview of Phase 3 trials:** Primary endpoints and timing for data readouts
  - COVID boosters & combinations
  - Flu vaccine
  - RSV vaccine
  - CMV vaccine

Proof-of-concept data from our sentinel programs de-risk our modalities and accelerate our development plans

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							Latent virus vaccines	*Respiratory vaccines*
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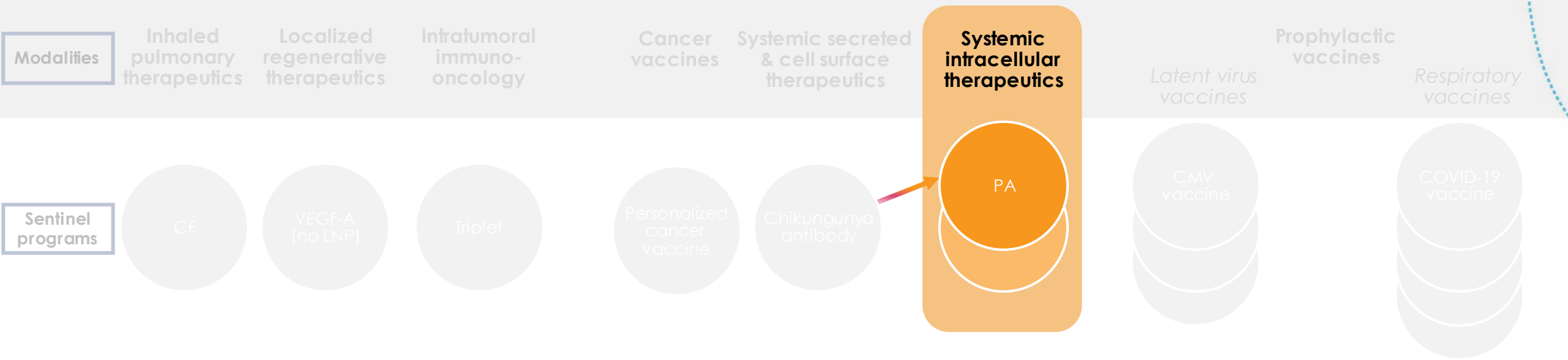
Increasing R&D investment

Proof-of-concept data from our sentinel programs de-risk our modalities and accelerate our development plans



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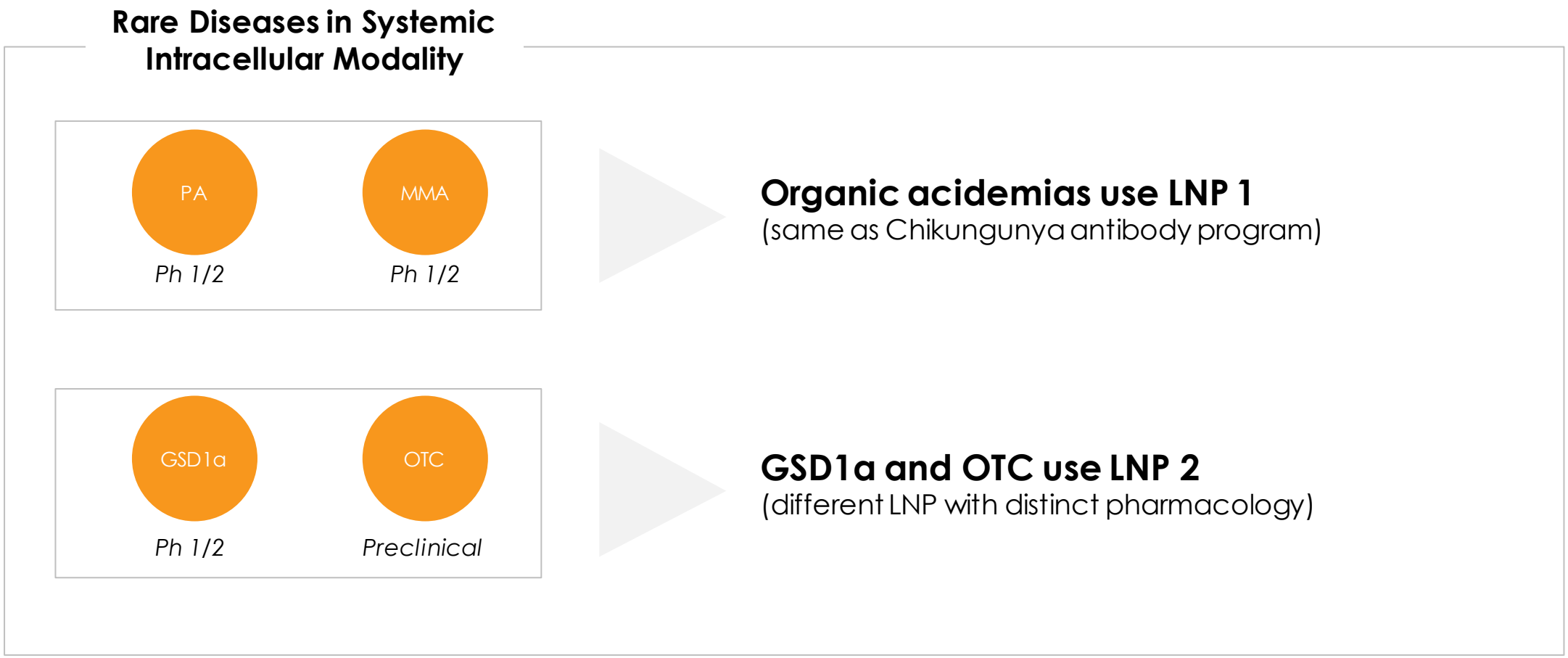
Increasing R&D investment

Moderna has two distinct LNP delivery systems dosing in rare disease clinical trials



Encouraging early clinical signs in rare disease modality

PA (mRNA-3927)

- 6 patient-years of experience on drug and **all participants eligible have decided to continue on Open Label Extension (OLE) Study**
- Generally **well-tolerated to date**
- **Reduction in biomarker** (3-HP levels) observed
- Encouraging data shows **decrease in the number of metabolic decompensation events (MDEs);** Initial discussions with regulators supportive of MDE as primary endpoint for a pivotal study

paramount study

GSD1a (mRNA-3745)

- Early data on **safety and pharmacodynamics are consistent and encouraging**
- In two patients, mRNA-3745 was **well tolerated to date**, and **showed extension of fast duration and normalization of glucose during fast**

balance TRIAL

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Dr. Mark S. Korson biography

Dr. Korson graduated in medicine from the University of Toronto and completed a pediatric residency at Toronto's Hospital for Sick Children, followed by a genetics/metabolism fellowship at Boston's Children's Hospital. He directed the metabolic clinics at Boston Children's Hospital until 2000 and across town at Tufts Medical Center until 2014. In 2007, he co-founded and continues to co-direct the SIMD's North American Metabolic Academy.

In 2017, Dr. Korson joined VMP Genetics as Director of Education and Physician Support Services, providing remote consultative assistance to clinicians at 10 major academic medical centers caring for patients with proven or suspected metabolic disease. He has significant experience in creating innovative educational resources about metabolic diseases for non-genetic clinicians so that they can play more of a role in patient diagnosis and management. Also at VMP Genetics, he directs the Patient-Teacher Registry and Patient-Teacher Video Catalog, with the aim of ensuring that the patient voice plays a bigger role in the education of health professionals. Regionally, Dr. Korson is on the board of the New England Regional Genetics Network, and as a founding board member of Rare New England, hosts the annual Rare Disease Day Speakers Series in New England and their online Medical Genetics Career Fairs.

Therapy for PA + MMA:
The need for something better

Mark S. Korson, MD

VMP Genetics

The story of PKU is the story of the specialty of metabolic disease


NO
ID
AMINO
ACID
AMINO
ACID
AMINO
ACID
AMINO
ACID
AMINO
ACID
AMINO
ACID
AMINO
ACID

PROTEIN

PHENYLALANINE

Phenylalanine hydroxylase

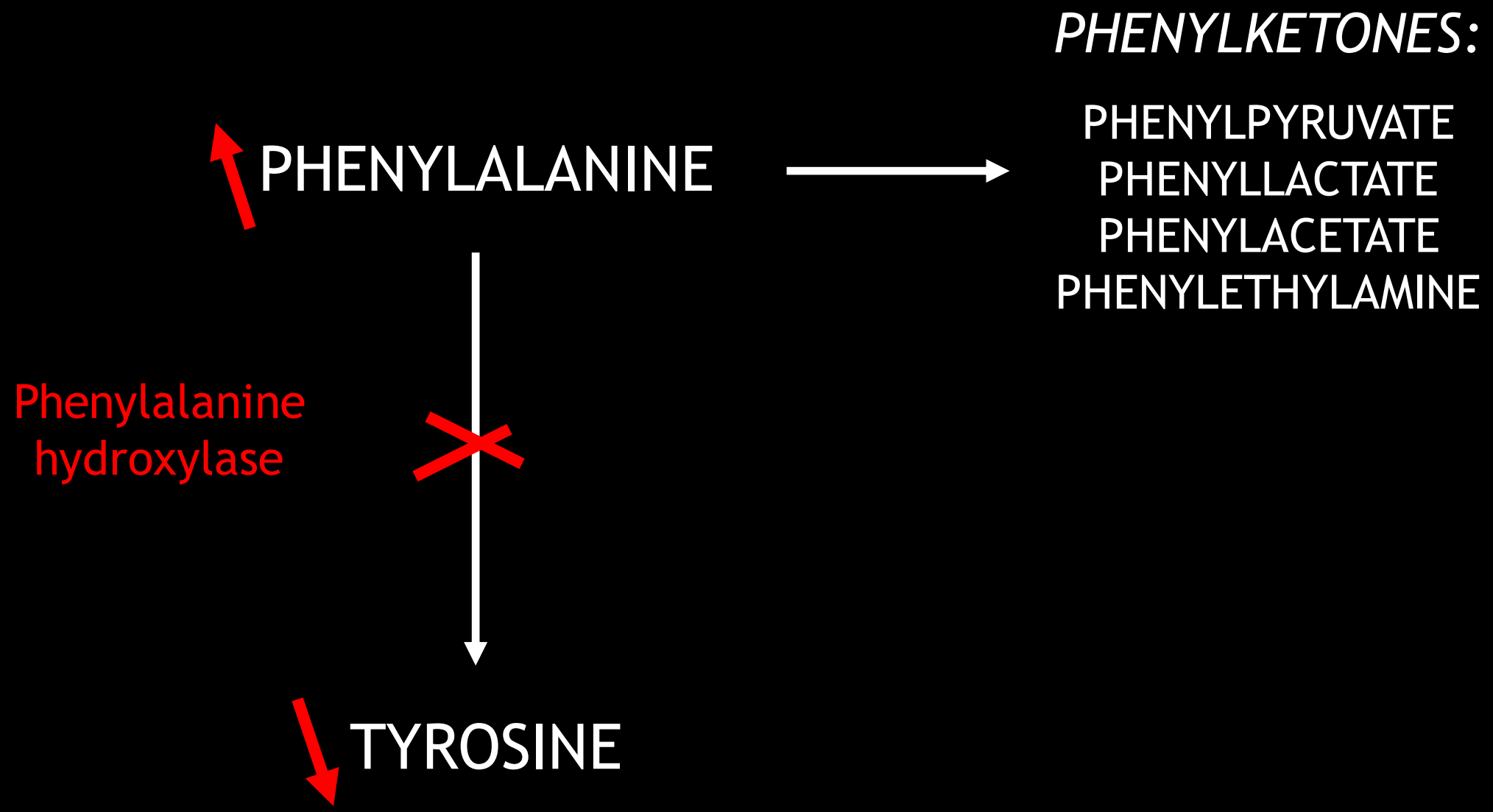
TYROSINE

PHENYLALANINE

Phenylalanine hydroxylase

TYROSINE

Dr. Asbjorn Folling, Norway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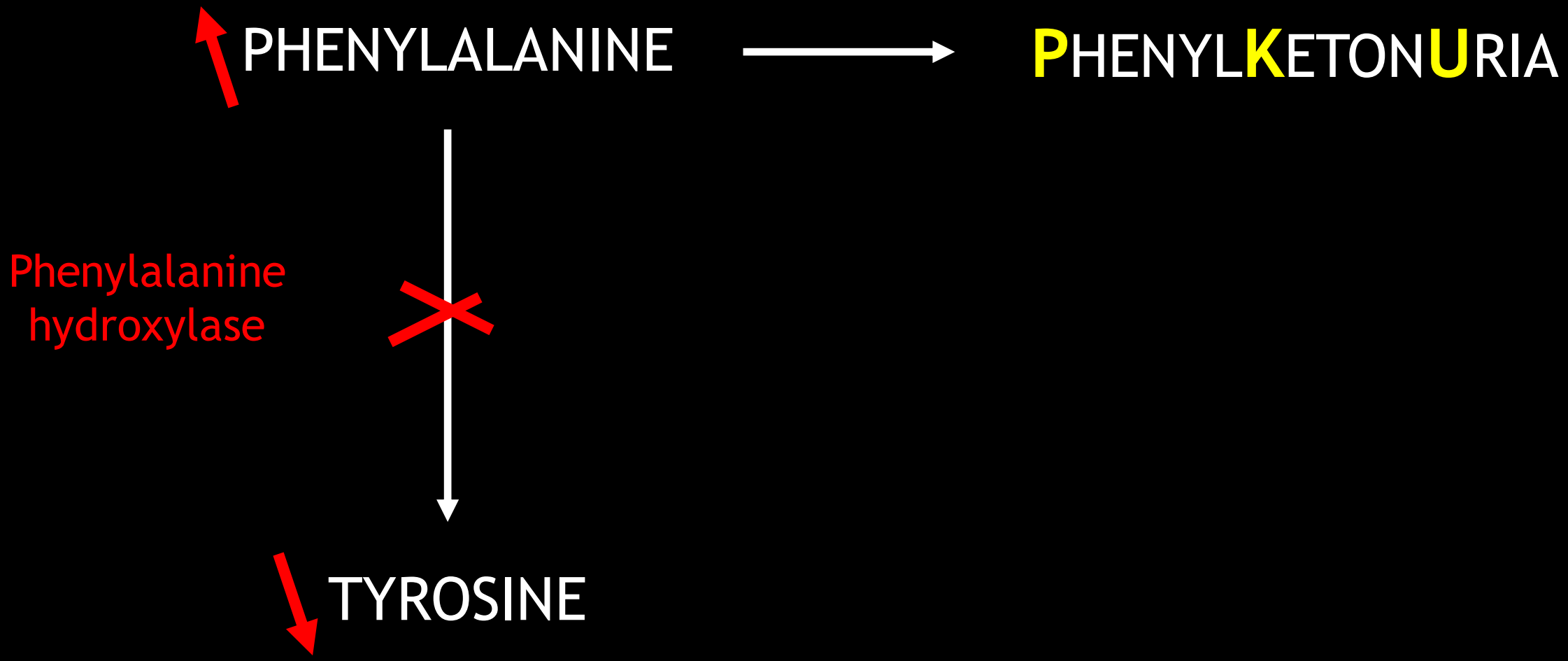
PHENYLETHYLAMINE
Phenylalanine hydroxylase
TYROSINE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PHENYLKETONURIA
Phenylalanine hydroxylase
TYROSINE

PHENYLKETONURIA (PKU)

Symptoms	Intellectual disability Seizures Psychiatric symptoms Lighter pigmentation of skin, hair Skin rash

PKU –
”schneiderzitzen”

PHENYLKETONURIA (PKU)

Pathophysiology

Intellectual disability	↑ PHE
Seizures	↑ PHE
Psychiatric symptoms	↑ PHE
Lighter pigmentation	↓ TYR
Skin rash	↓ TYR

A DIETARY APPROACH TO METABOLIC DISEASE

Horst Bickel (1954) proposed a low PHE diet

2 year old girl with PKU:

- PHE dropped
- Phenylketones cleared
- Improved in developmental tasks

A DIETARY APPROACH TO METABOLIC DISEASE

Horst Bickel (1954) proposed a low PHE diet

2 year old girl with PKU:

- Reversed when restarted on a high PHE diet

DIETARY THERAPY

SUBSTRATE RESTRICTION – PKU

- Restricting natural protein → inadequate protein intake

DIETARY THERAPY

SUBSTRATE RESTRICTION - PKU

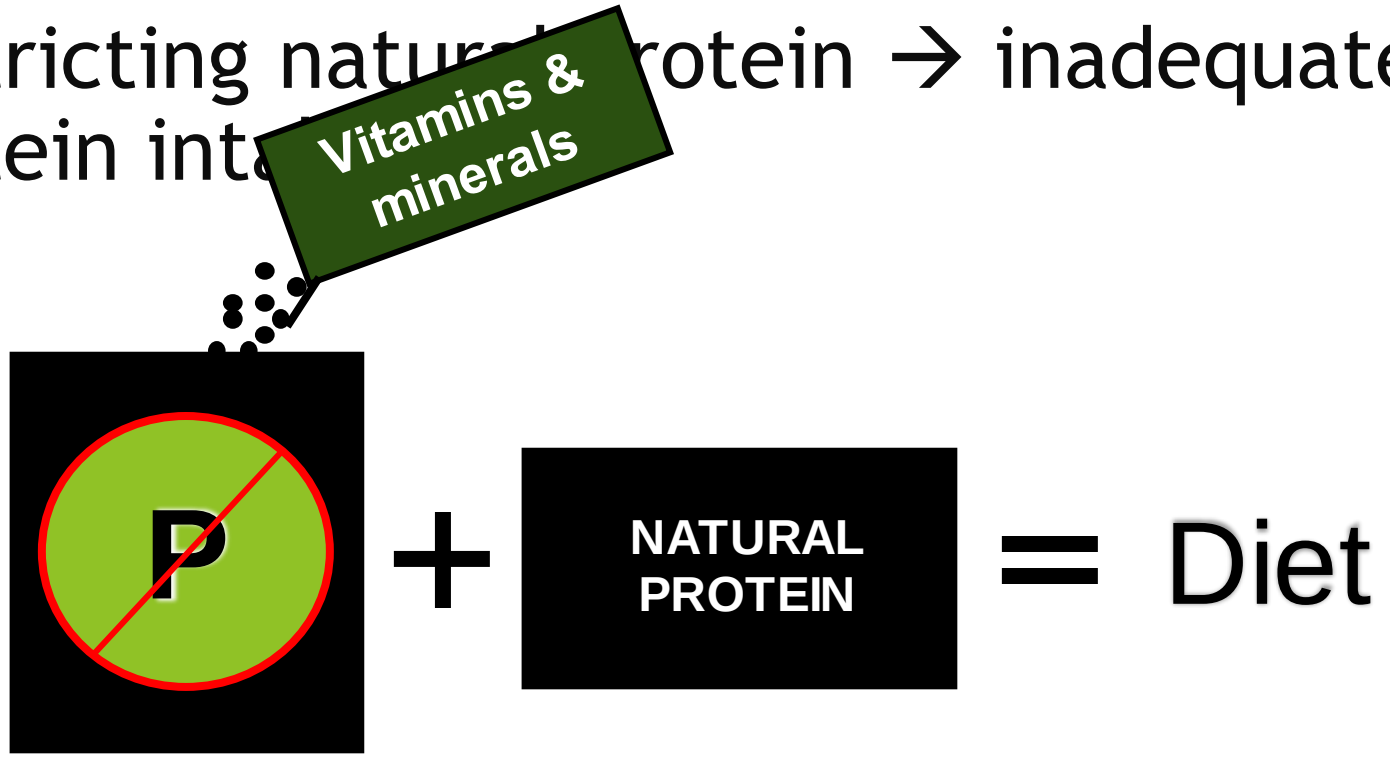
- Restricting natural protein → inadequate protein intake

No PHE

DIETARY THERAPY

SUBSTRATE RESTRICTION - PKU

- Restricting natural protein → inadequate protein int



Foods forbidden from amino acid-restricted diets

Permitted - fruit

Permitted - vegetables

Permitted - foods lower in protein content

THE PKU DIET, circa 1980s

A FEW ‘LOW PROTEIN’ FOODS

RECOMMENDED UNIFORM SCREENING PANEL - 2022

Amino acid disorders

Phenylketonuria
Homocystinuria
Maple syrup urine disease
Tyrosinemia type I
Citrullinemia type I
Argininosuccinic aciduria

Organic acid disorders

Propionic acidemia
Methylmalonic acidemia (MMA, mutase)
MMA (cobalamin disorders)
Isovaleric acidemia
Beta-ketothiolase deficiency
Holocarboxylase synthetase def'y
Glutaric acidemia type I
3-MC carboxylase deficiency
Biotinidase deficiency
HMG CoA lyase deficiency

Fatty acid oxidation defects

MCAD deficiency
VLCAD deficiency
LCHAD deficiency
Trifunctional protein deficiency
Carnitine uptake defect

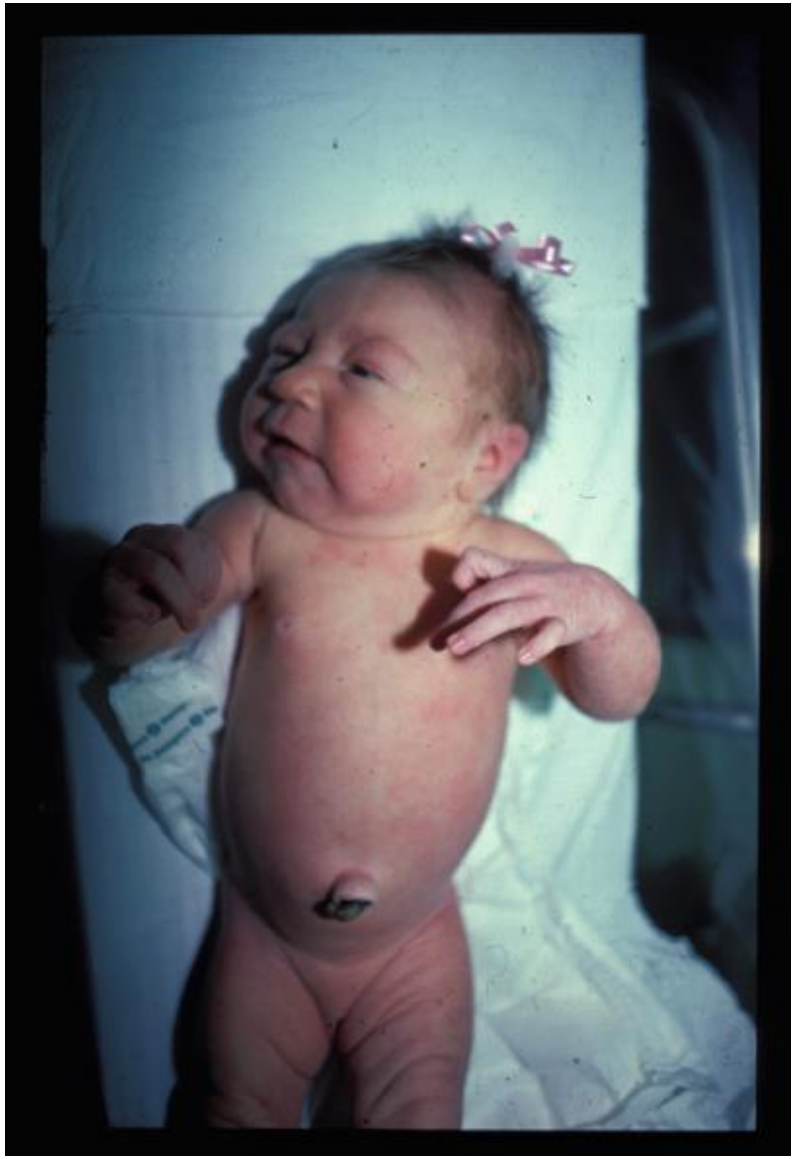
Other Metabolic disorders

Galactosemia
Pompe disease
Hurler disease (MPS I)
X-linked adrenoleukodystrophy

Other disorders

Congenital hypothyroidism
Congenital adrenal hyperplasia
Hemoglobinopathies (3)
Cystic fibrosis
Severe combined immunodeficiencies
Critical congenital heart disease
Hearing loss
Spinal muscular atrophy

SUCCESS OF PKU SCREENING → MATERNAL PKU



Cognitive/motor disability (92%)

Small head (73%)

In utero growth retardation (40%)

Heart defects (15%)

INADEQUATE PKU MANAGEMENT

Executive function problems

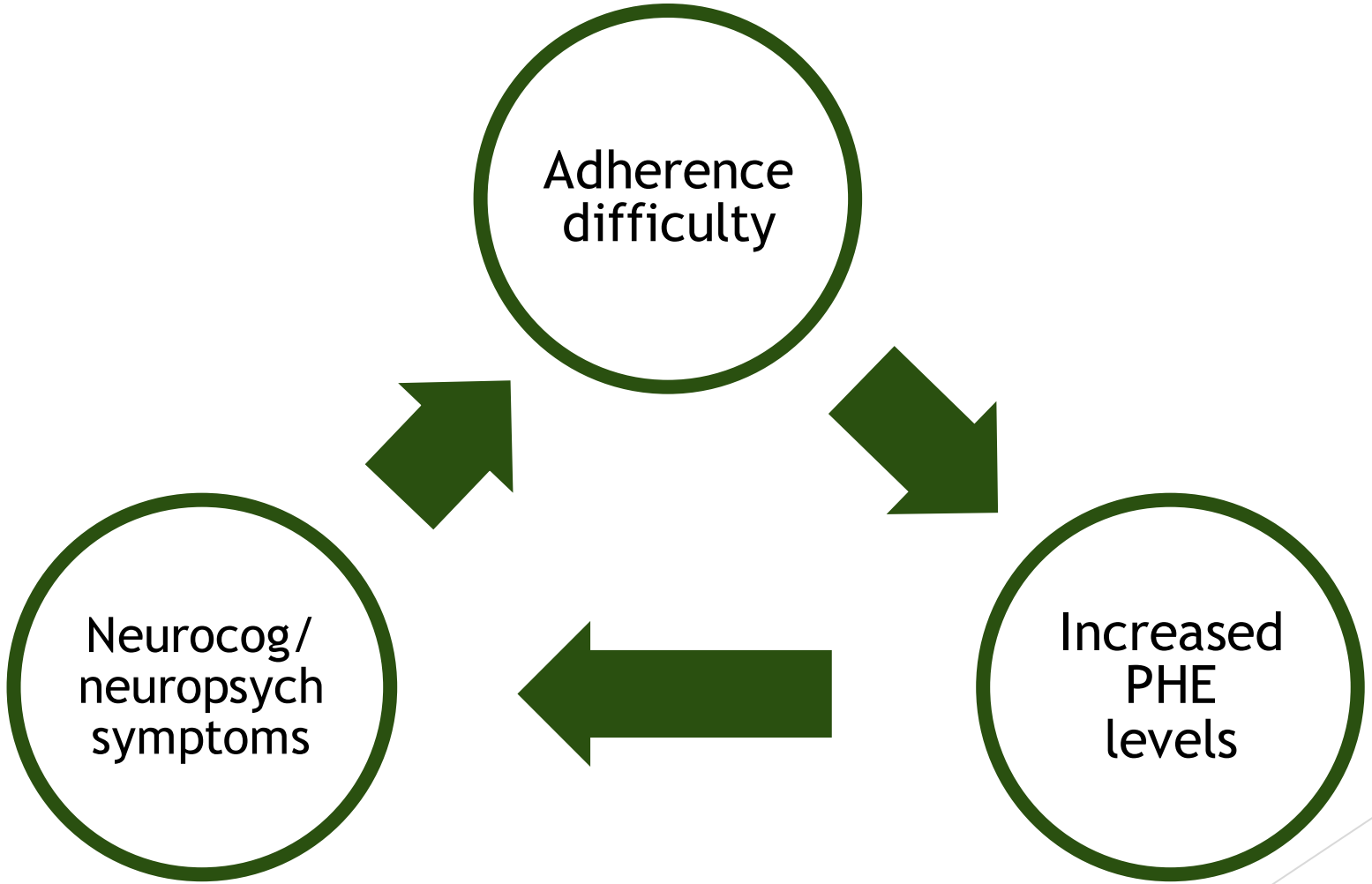
- Inattention
- Cognitive rigidity
- Lack of impulse control

Psychiatric symptoms

- Anxiety
- Depression
- Phobia

Issues with relationships

CHALLENGES TO MANAGEMENT



Adapted from Brittany Holmes

PROBLEM!

Survey of 3772 patients with PKU (US):

- % of patients who have elevated PHE levels
  - 18-29 yr = ~ 62%
  - 30 yr and older = ~ 71%
- Adherence to PHE level monitoring
  - 37% of adults 30 + older up test once a year or less

Jurecki et al, 2017

88% of adults with PKU are unable to adhere to a PHE-restricted diet

Hardy et al, 2018

PROBLEM!

Age (years)	Total phenylketonuria patients based on incidence of 1:12,707 (*n*)	Phenylketonuria patients reported in the clinic (*n*)	Estimated not in the clinic, *n* (%)
0–4	1,677	1,357	320 (19)
5–12	2,598	1,924	674 (26)
13–18	1,977	1,306	671 (34)
19–24	1,993	1,036	957 (48)
25–45	6,741	1,557	5,184 (77)
Total	14,988	7,180	7,808 (52)

Berry et al, 2013

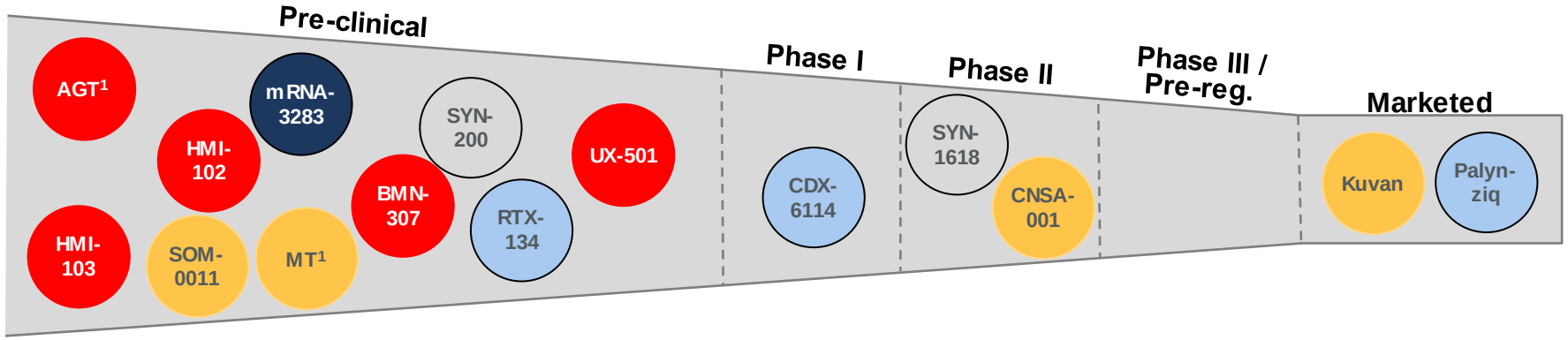
WHAT DO PATIENTS WANT?

Survey by National PKU Alliance (625 patients)

- 77.7% - most desired lifestyle improvement:
- “To be able to increase my protein intake without increasing my symptoms of PKU”

Brown CS + Lichter-Konecki U, 2015

PKU: from preclinical to marketed products



Pre-clinical	
SYN-200	Microbiome PAL LAAD
RTX-134	PAL in red blood cell as cargo
SOM-0011	*Unidentified Activity*
AGT1	Lentiviral based GT
BMN-307	*AAV5-PAH GT*
HMI-102	Adult indication, AAV-PAH GT
HMI-103	Ped. indication, AAV-PAH GT
UX-501	AAV8-PAH GT
mRNA-3283	PAH mRNA
MT 1	Small Molecule

Phase I	
CDX-6114	GI-stable PAL variant enzyme

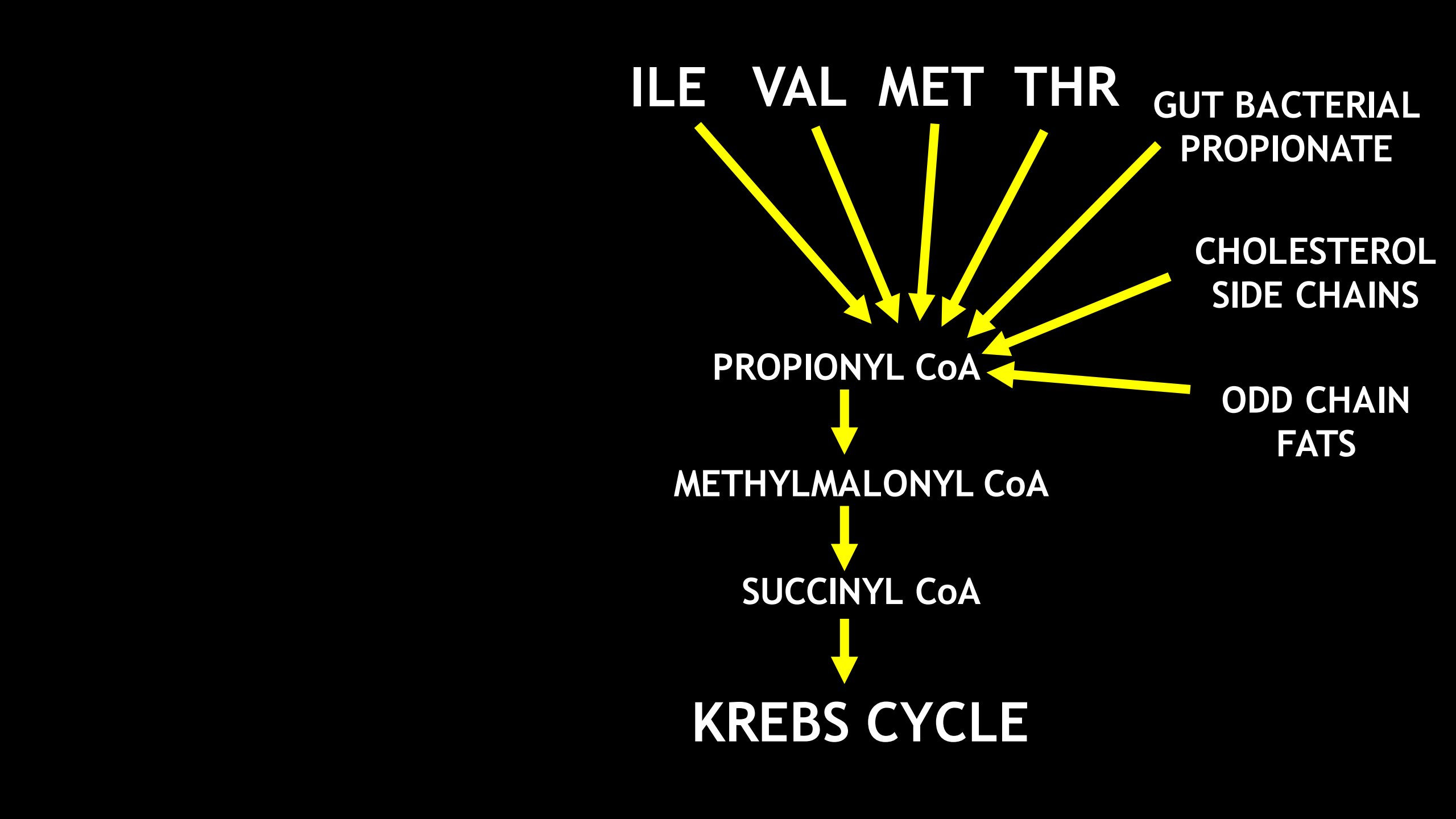
Phase II	
SYN-1618	Microbiome Ecoli Nissle PAL LAAD
CNSA-001	Oral synthetic sepiapterin

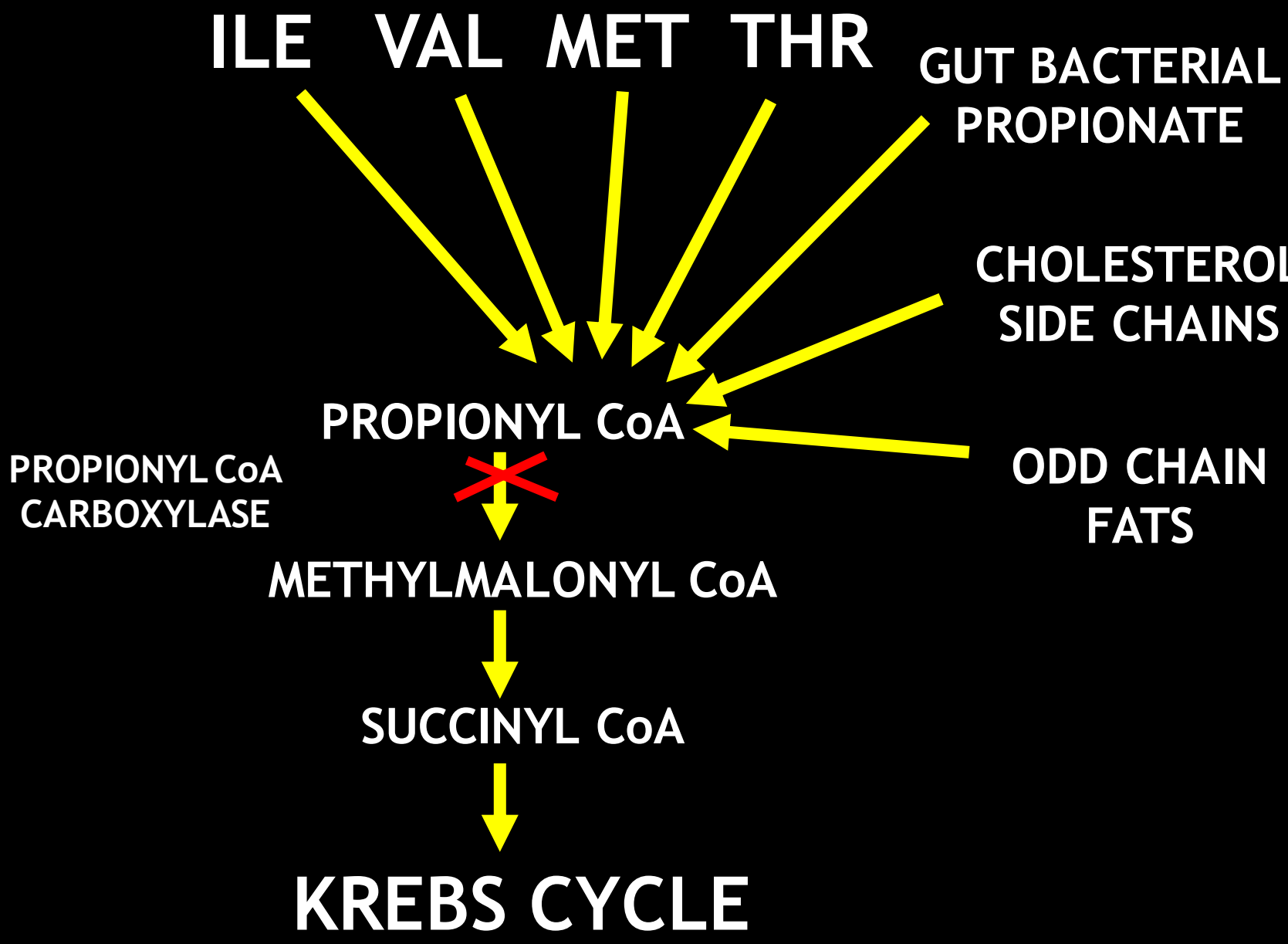
Phase III / Pre-reg.
No Assets Currently in P3 or Pre-Registration Phases

Marketed	
Kuvan	Synthetic BH_4 co-factor
Note: 20 – 56% response rate	
Palynziq	Recombinant bacterial PAL
Note: Associated with severe anaphylaxis	

Key:
- microbiome
- Biologic
- Small Molecule
- Gene Therapy
- mRNA

Why am I talking to you about PKU??


ILE
VAL
MET
THR
GUT BACTERIAL PROPIONATE
CHOLESTEROL SIDE CHAINS
ODD CHAIN FATS
PROPIONYL CoA
METHYLMALONYL CoA
SUCCINYL CoA
KREBS CYCLE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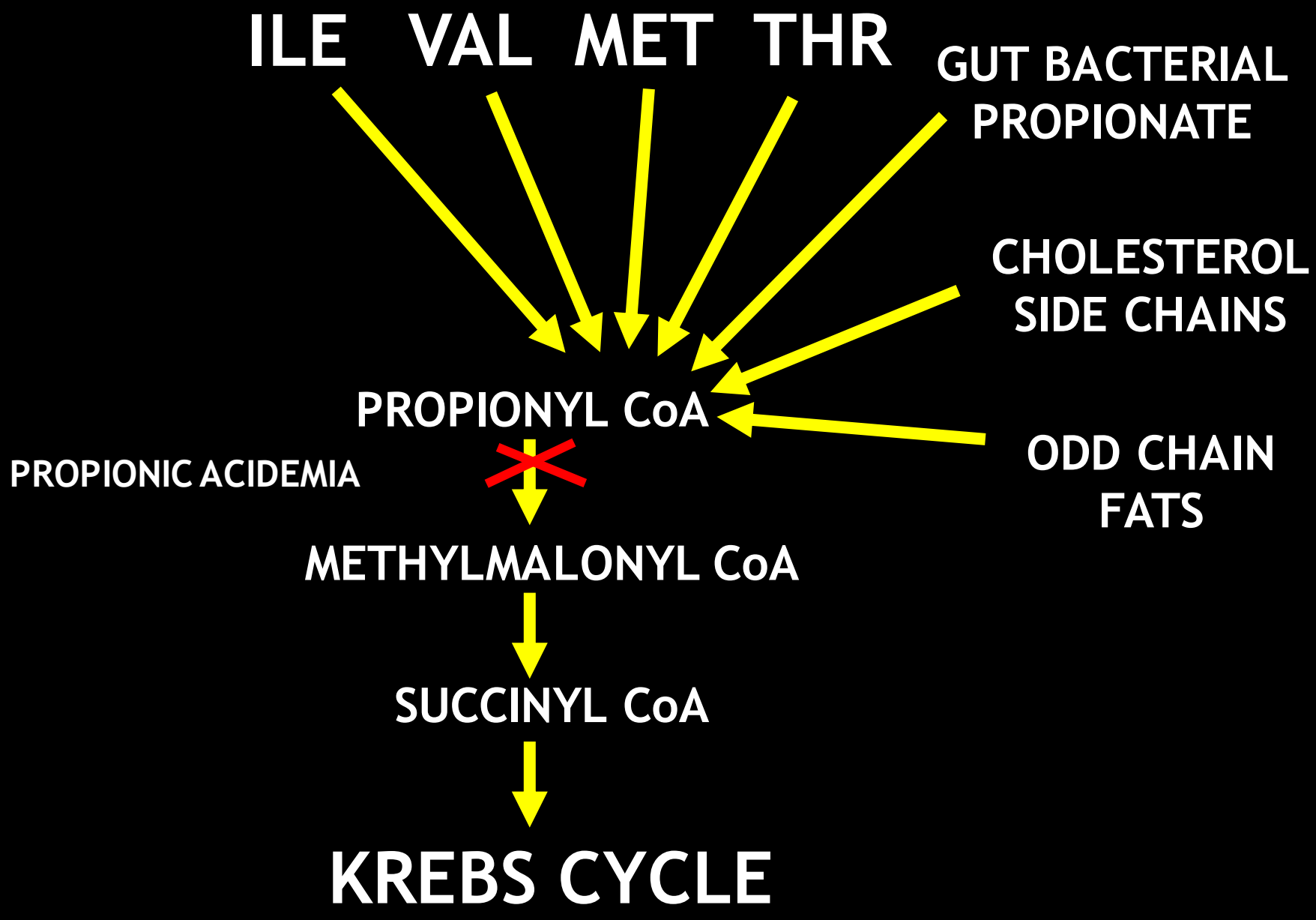
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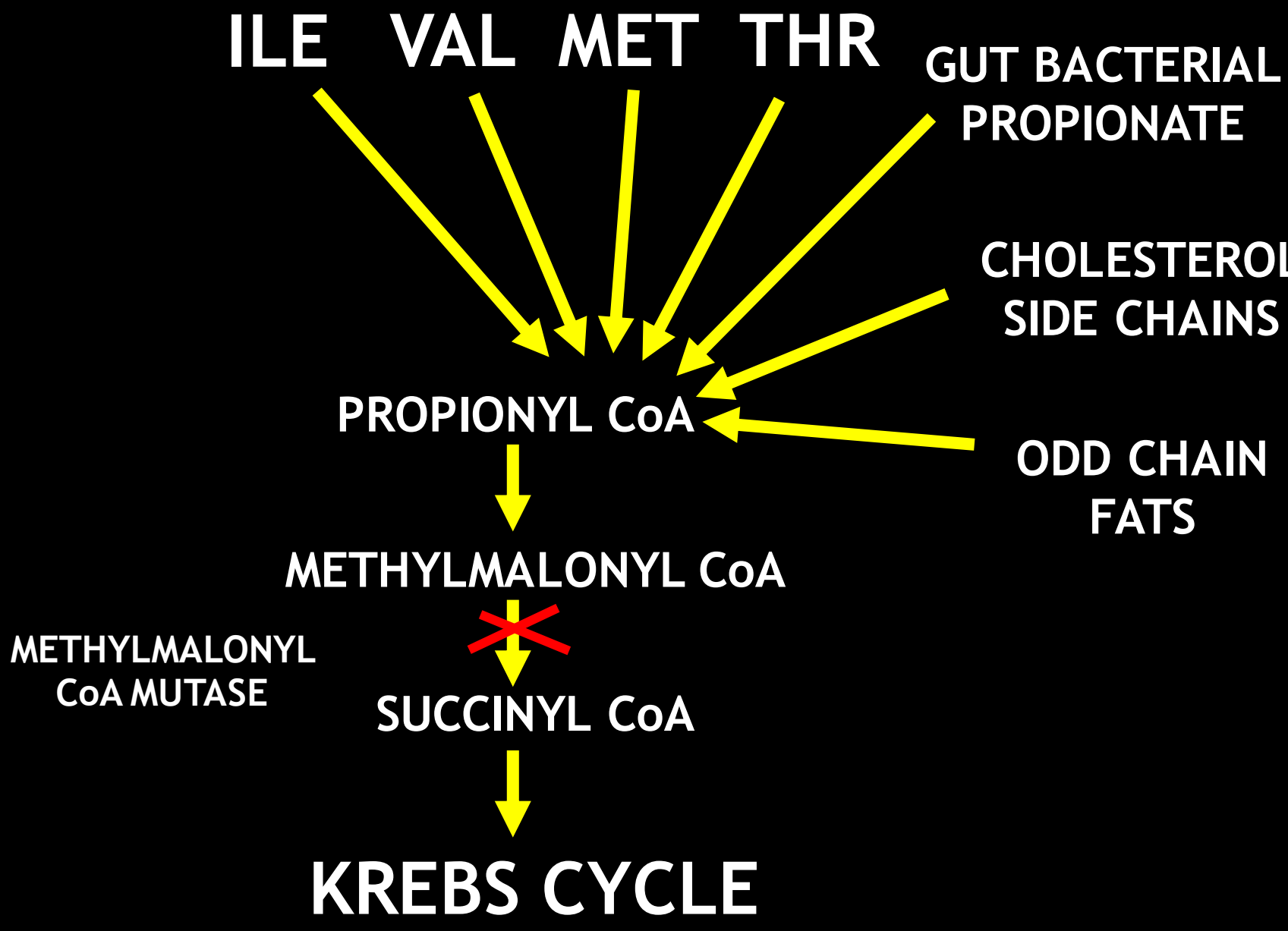
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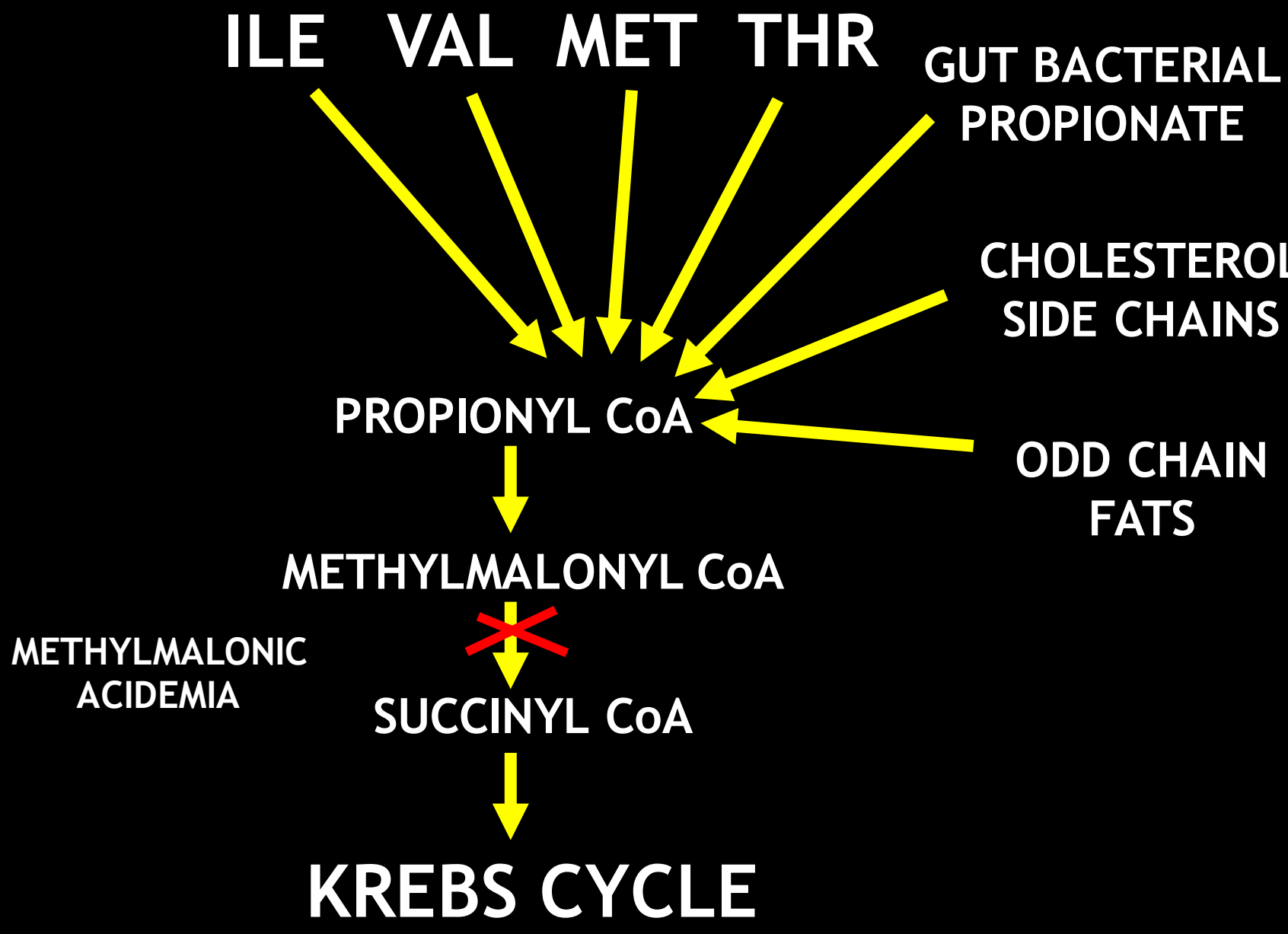
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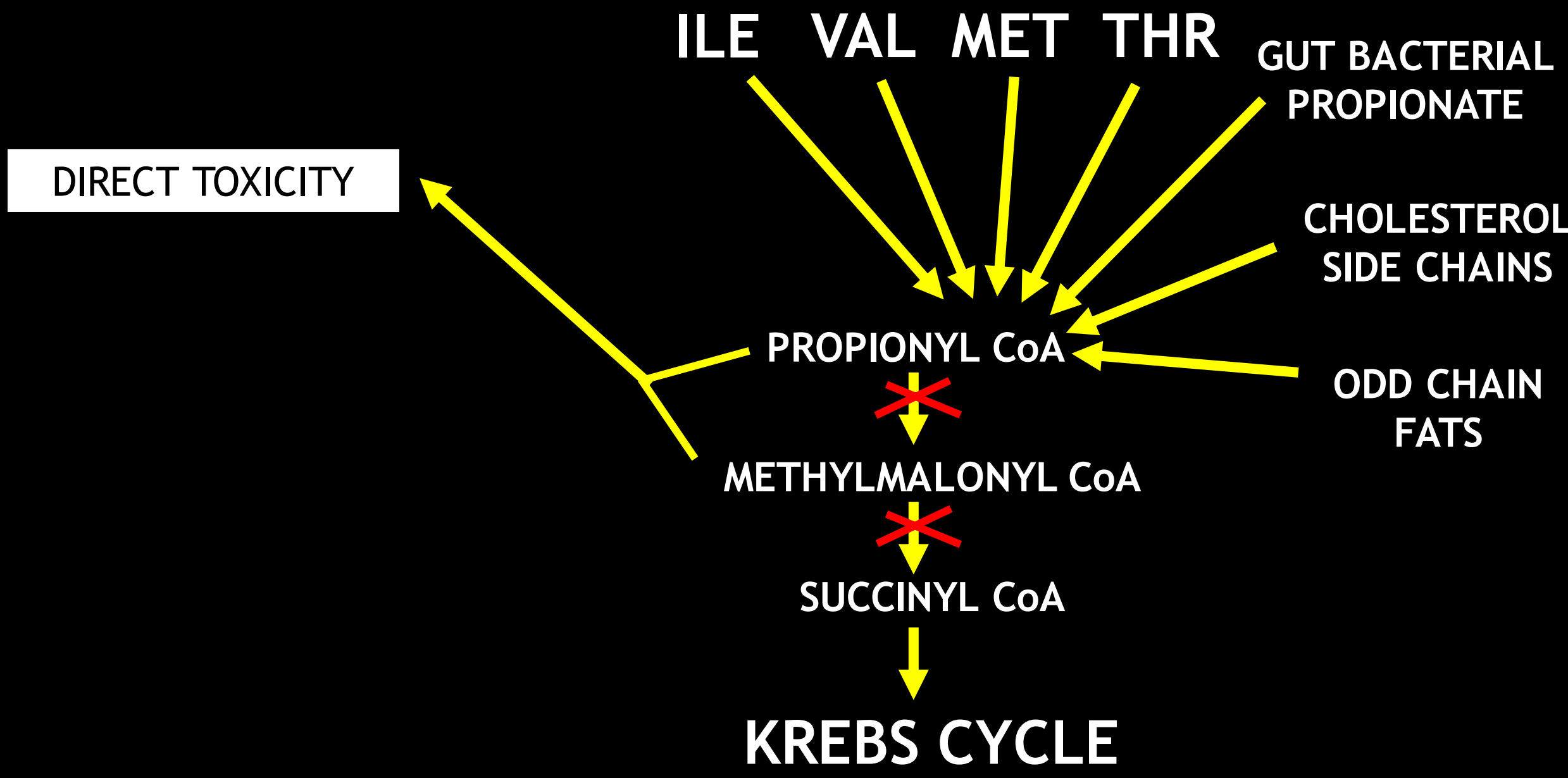
KREBS CYCLE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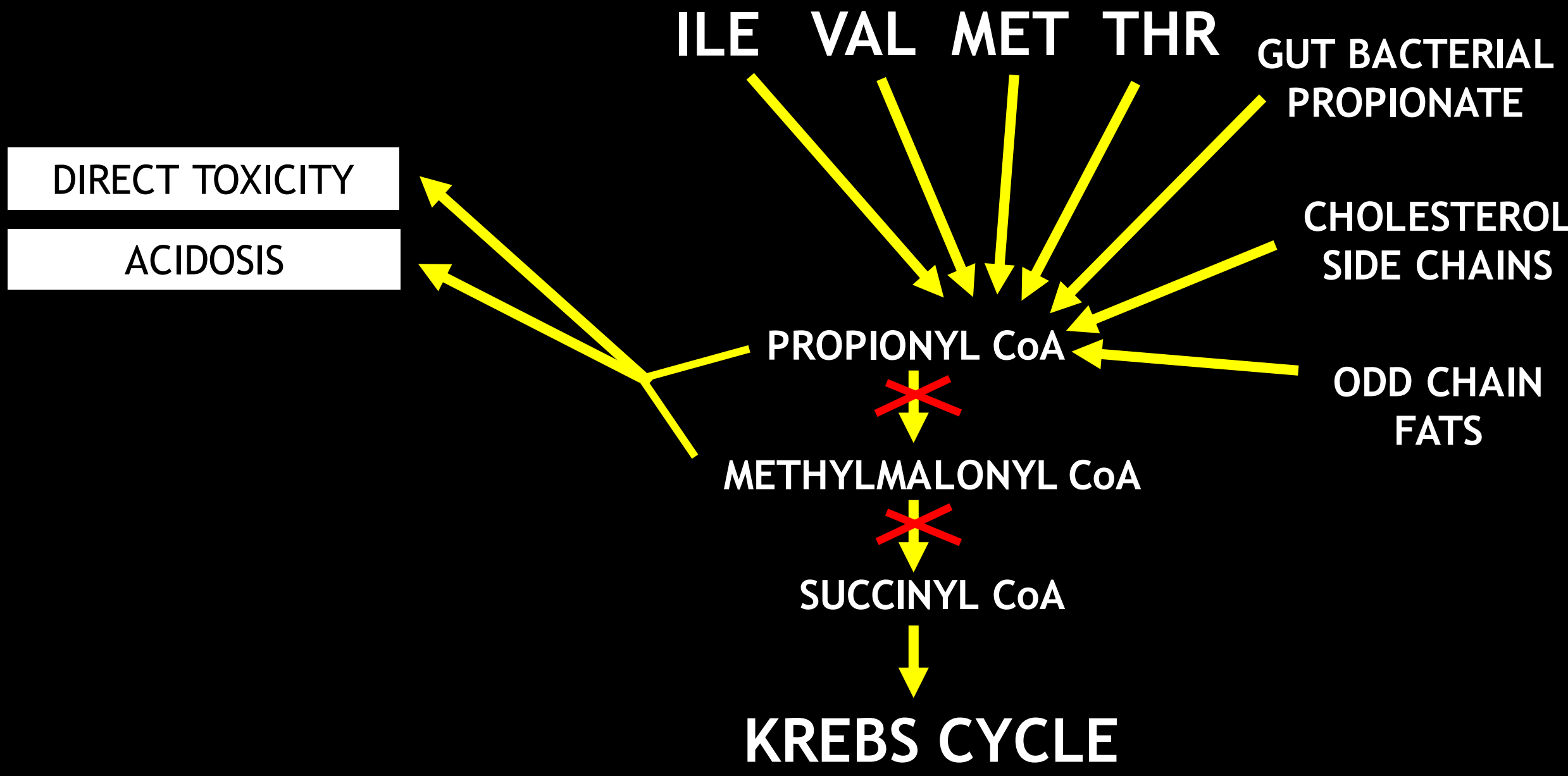
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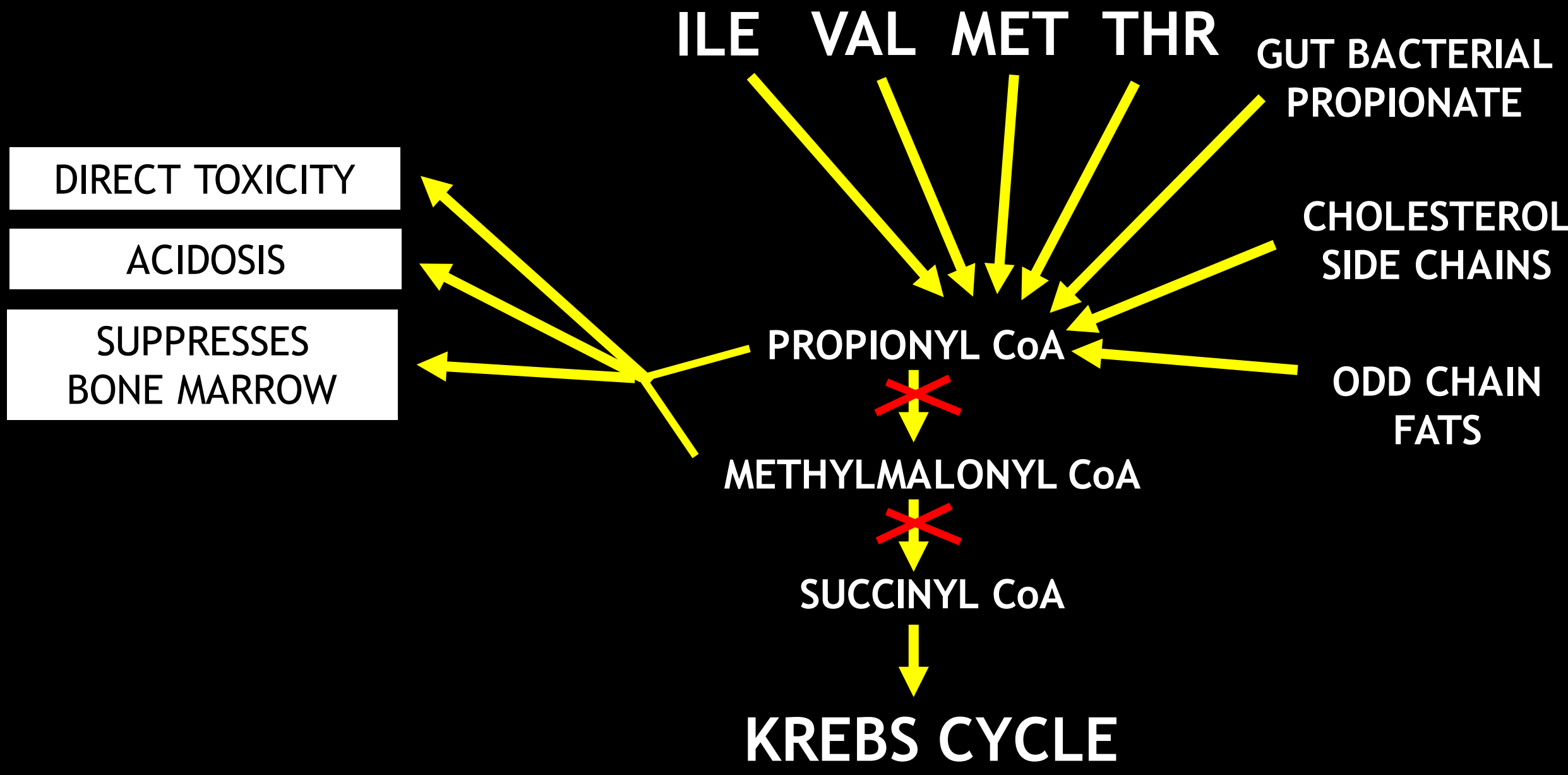
KREBS CYCLE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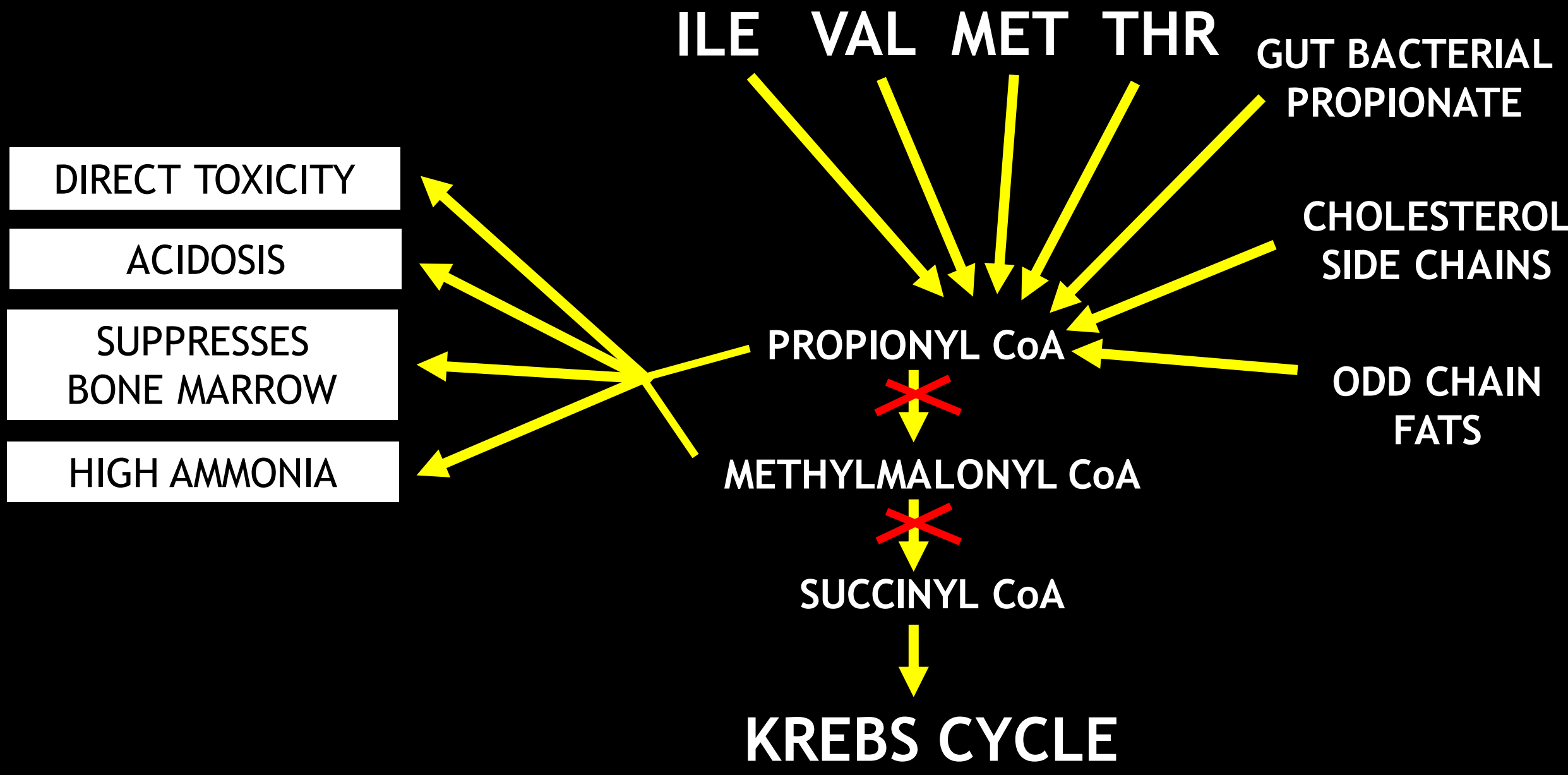
DIRECT TOXICITY
ACIDOSIS
SUPPRESSES BONE MARROW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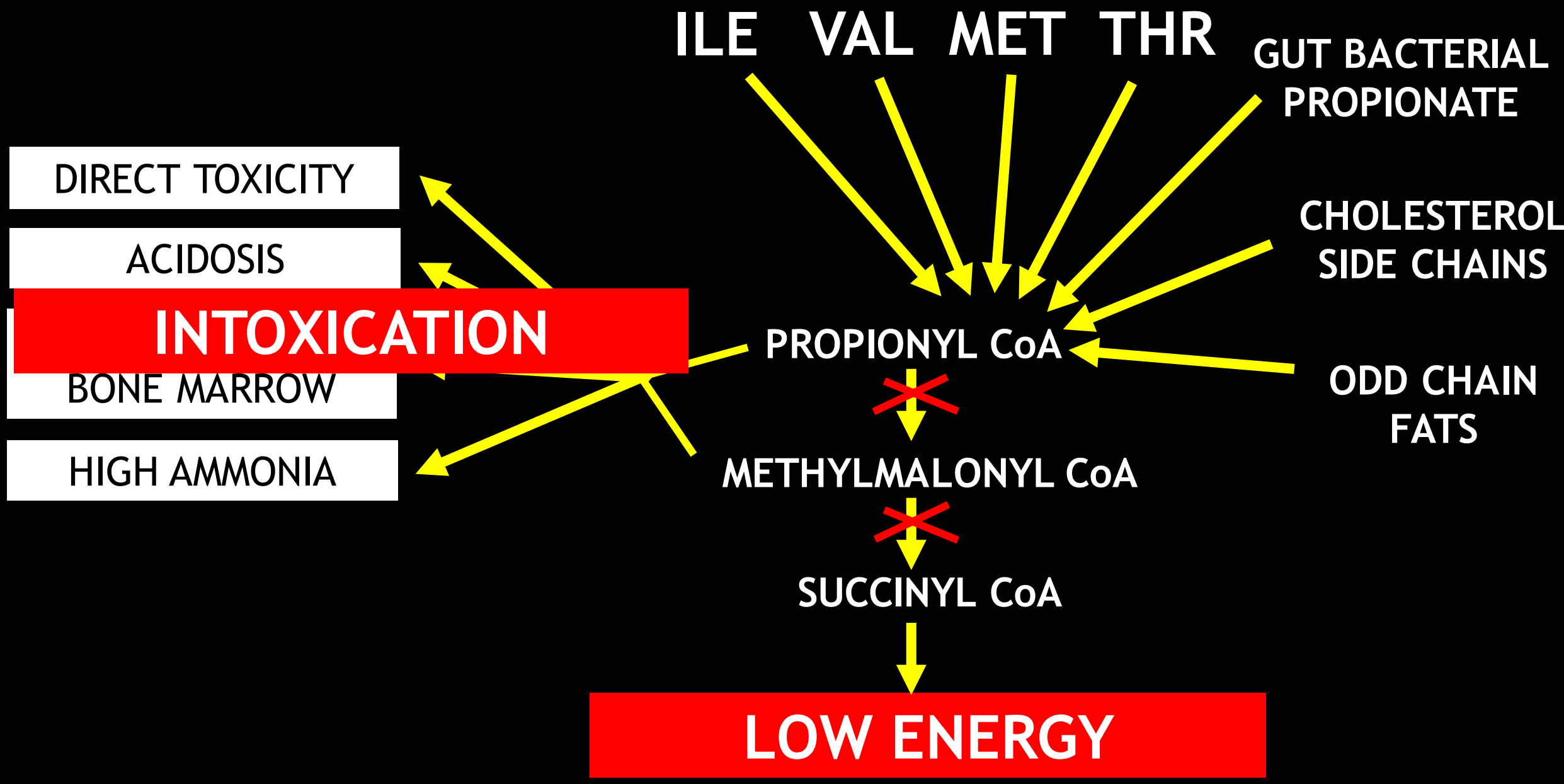
KREBS CYCLE
DIRECT TOXICITY
ACIDOSIS
SUPPRESSES BONE MARROW
HIGH AMMONIA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METHYLMALONYL CoA
SUCCINYL CoA
LOW ENERGY
INTOXICATION
DIRECT TOXICITY
ACIDOSIS
BONE MARROW
HIGH AMMONIA

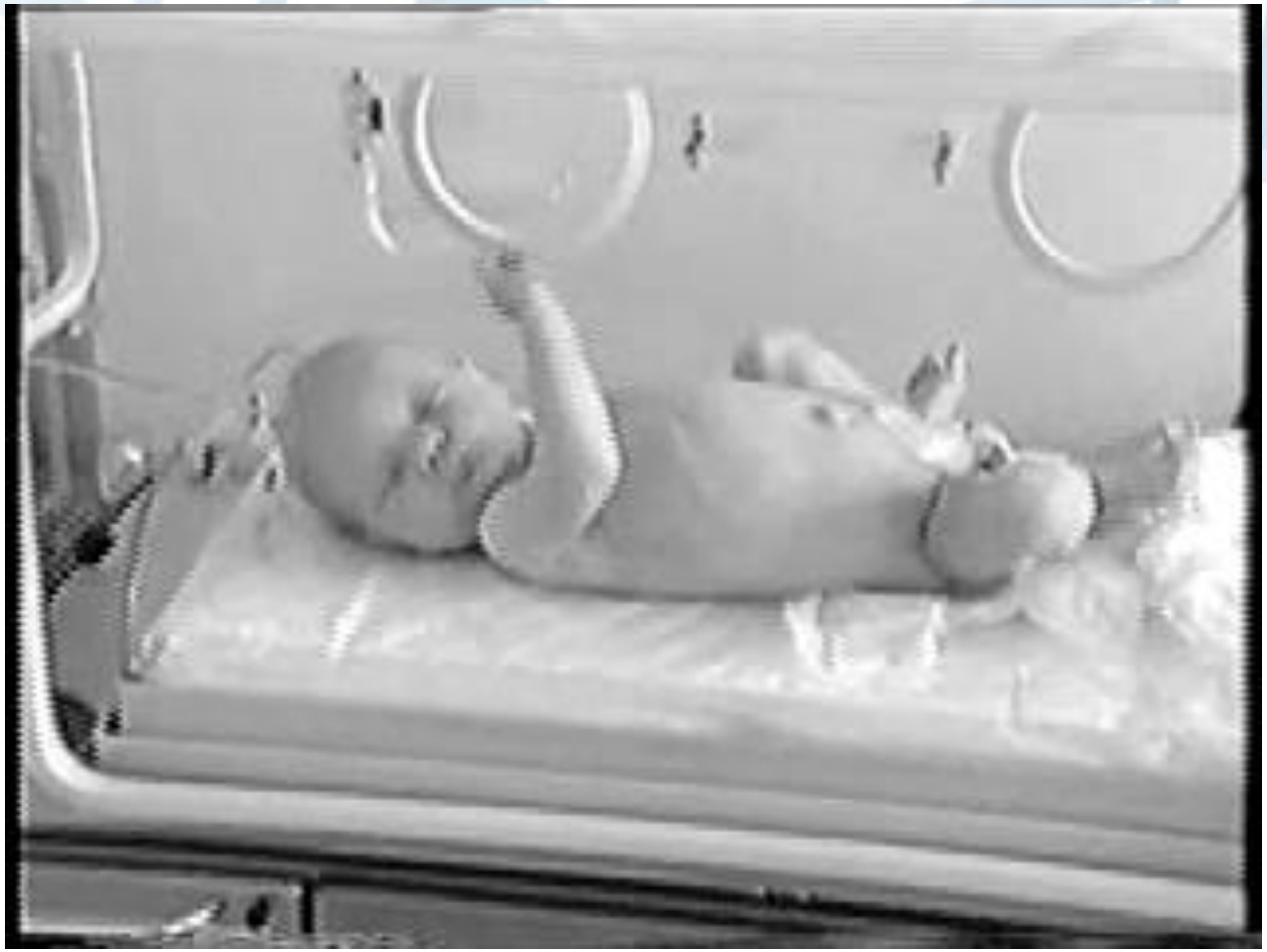
METABOLIC CRISIS (*aka* **M**etabolic **D**ecompensation **E**vent)

Symptoms	Poor feeding, vomiting → dehydration Lethargy, altered consciousness → coma Looks “septic”

PROGRESSION OF A METABOLIC CRISIS

Advanced stage	Apnea Slowing heart rate Seizures Hypothermia Generalized organ dysfunction Stroke Sudden death

Movements — Infant with an Organic Acidemia



Video from JM Saudubray and Thierry Billette de Vilmeur

ISOLATED MMA + PA – CLINICAL SYNDROMES (1)

Neonatal	Coma due to high ammonia Bone marrow suppression → infection Intracranial hemorrhage Diabetes mellitus Infantile spasms

Adapted from C. Venditti, 2020

ISOLATED MMA + PA – CLINICAL SYNDROMES (2)

Infancy/early childhood	“Pure” neurologic syndromes “Brain dysfunction” Movement disorder, unsteady gait Pancreatitis Infection → crisis + multiorgan failure Diabetic ketoacidosis ”Stroke”

Adapted from C. Venditti, 2020

ISOLATED MMA + PA – CLINICAL SYNDROMES (3)

Adolescence	Mental status changes Cardiac muscle failure (cardiomyopathy) Cardiac arrest

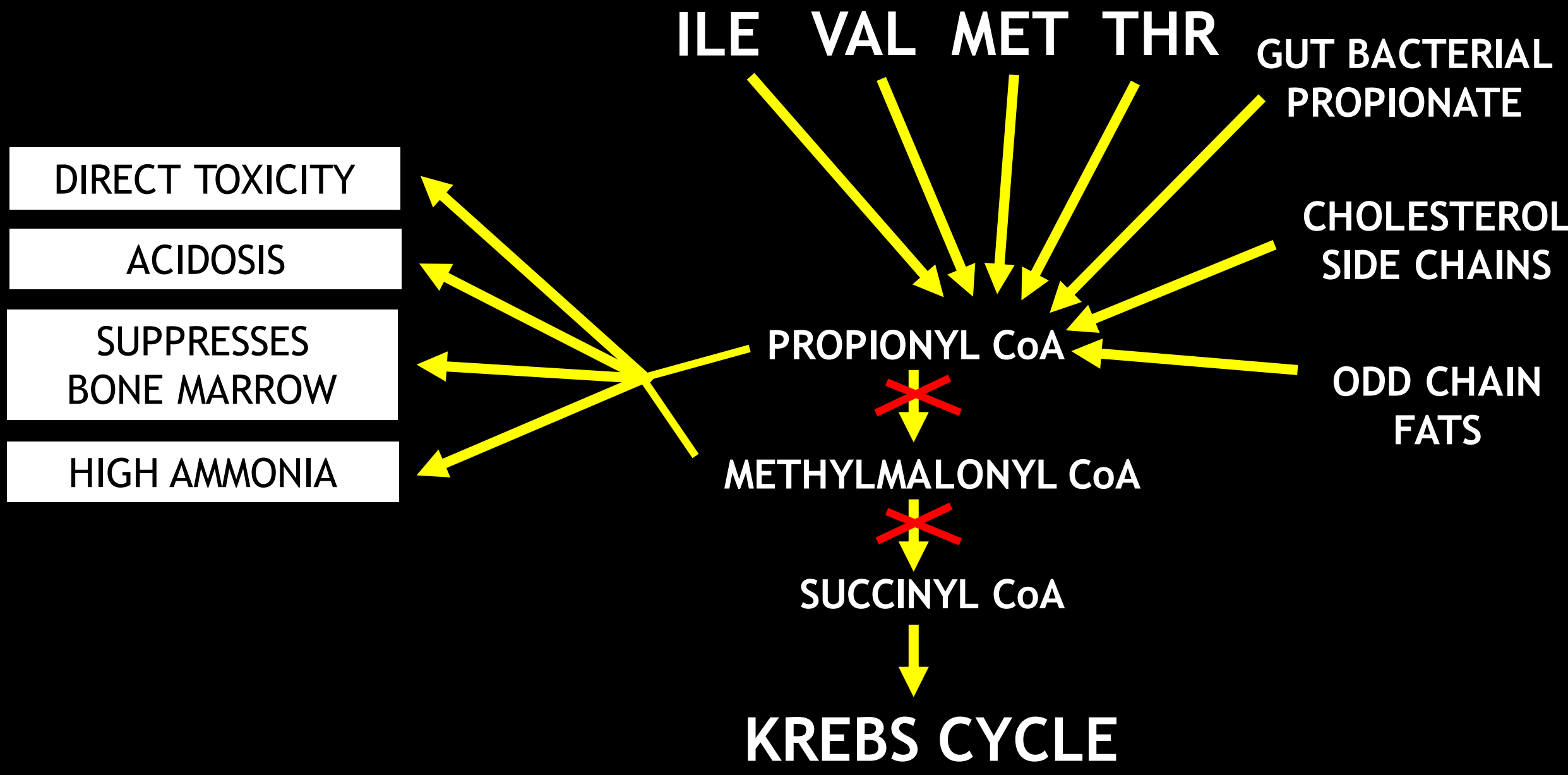
Adapted from C. Venditti, 2020

ISOLATED MMA + PA – CLINICAL SYNDROMES (4)

Adult	Movement disorder Cardiomyopathy Isolated kidney disease Optic nerve atrophy → blindness

Adapted from C. Venditti, 2020

HOW PA + MMA PATIENTS ARE MANAGED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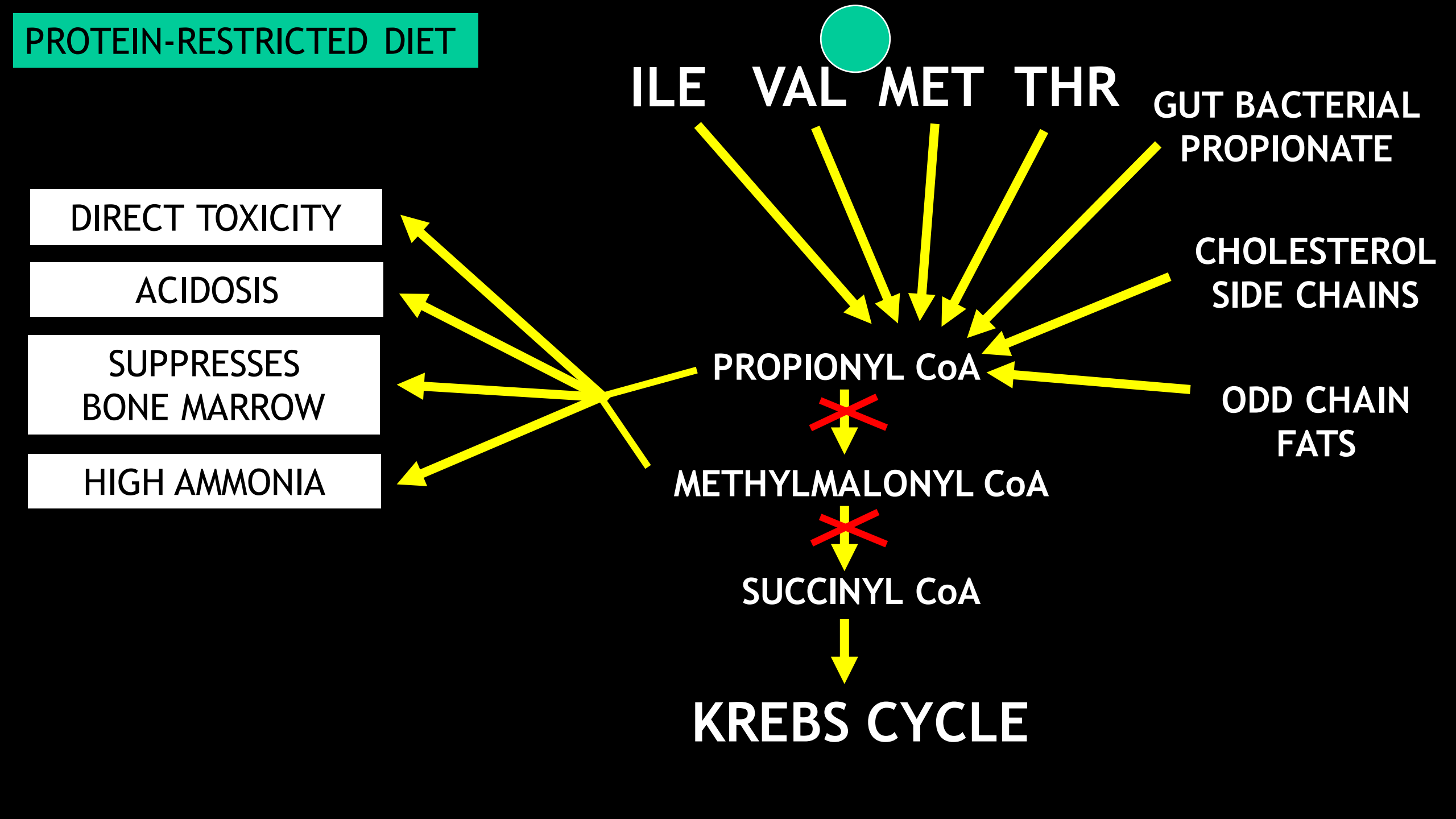
METHYLMALONYL CoA
SUCCINYL CoA
KREBS CYCLE
DIRECT TOXICITY
ACIDOSIS
SUPPRESSES BONE MARROW
HIGH AMMONIA

PROTEIN-RESTRICTED DIET

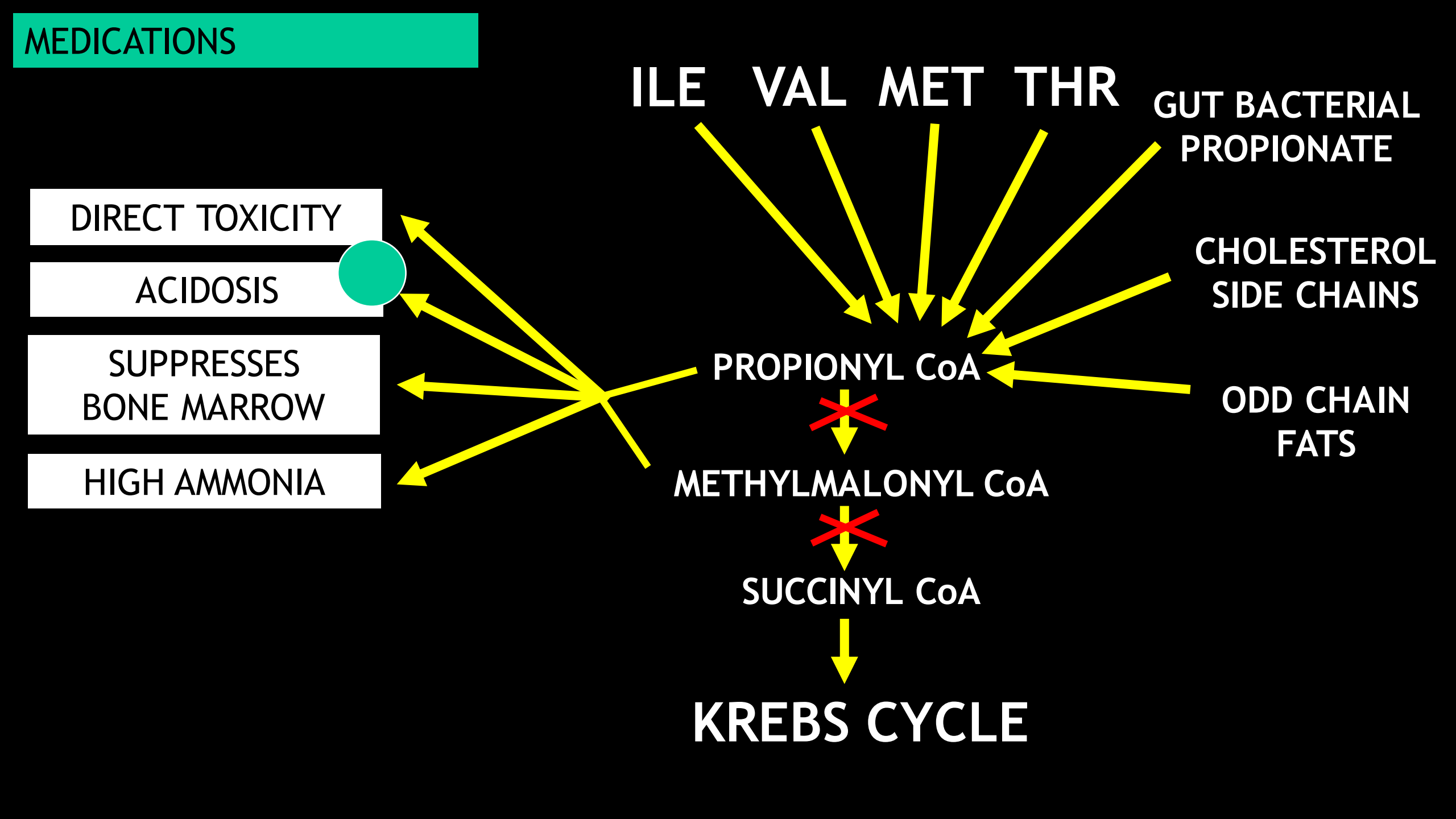


DIETARY THERAPY

SUBSTRATE RESTRICTION - PA+MMA

- Restricting natural protein → inadequate protein intake

No VAL, ILE, THR, MET


MEDICATIONS
ILE VAL MET THR
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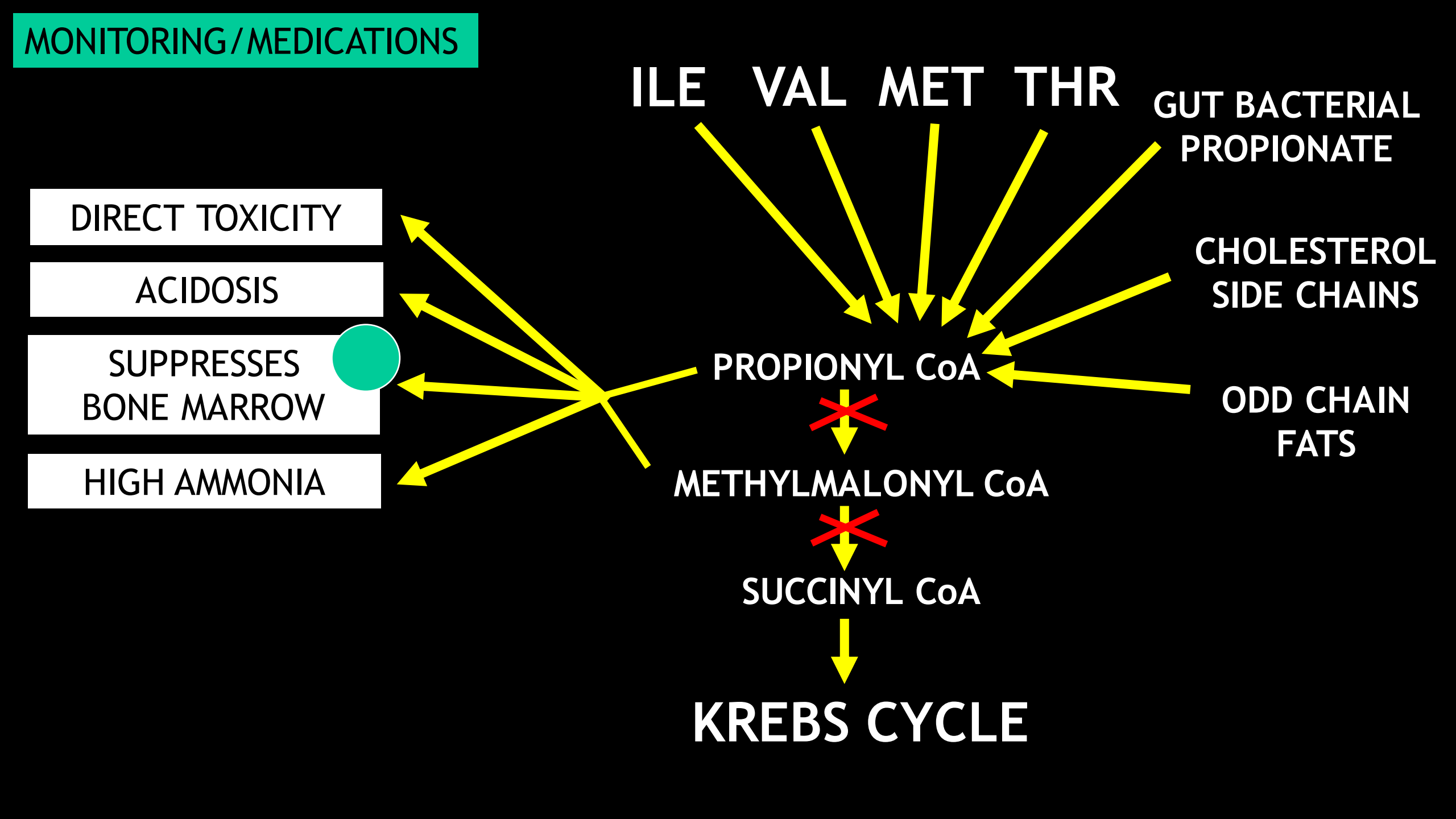
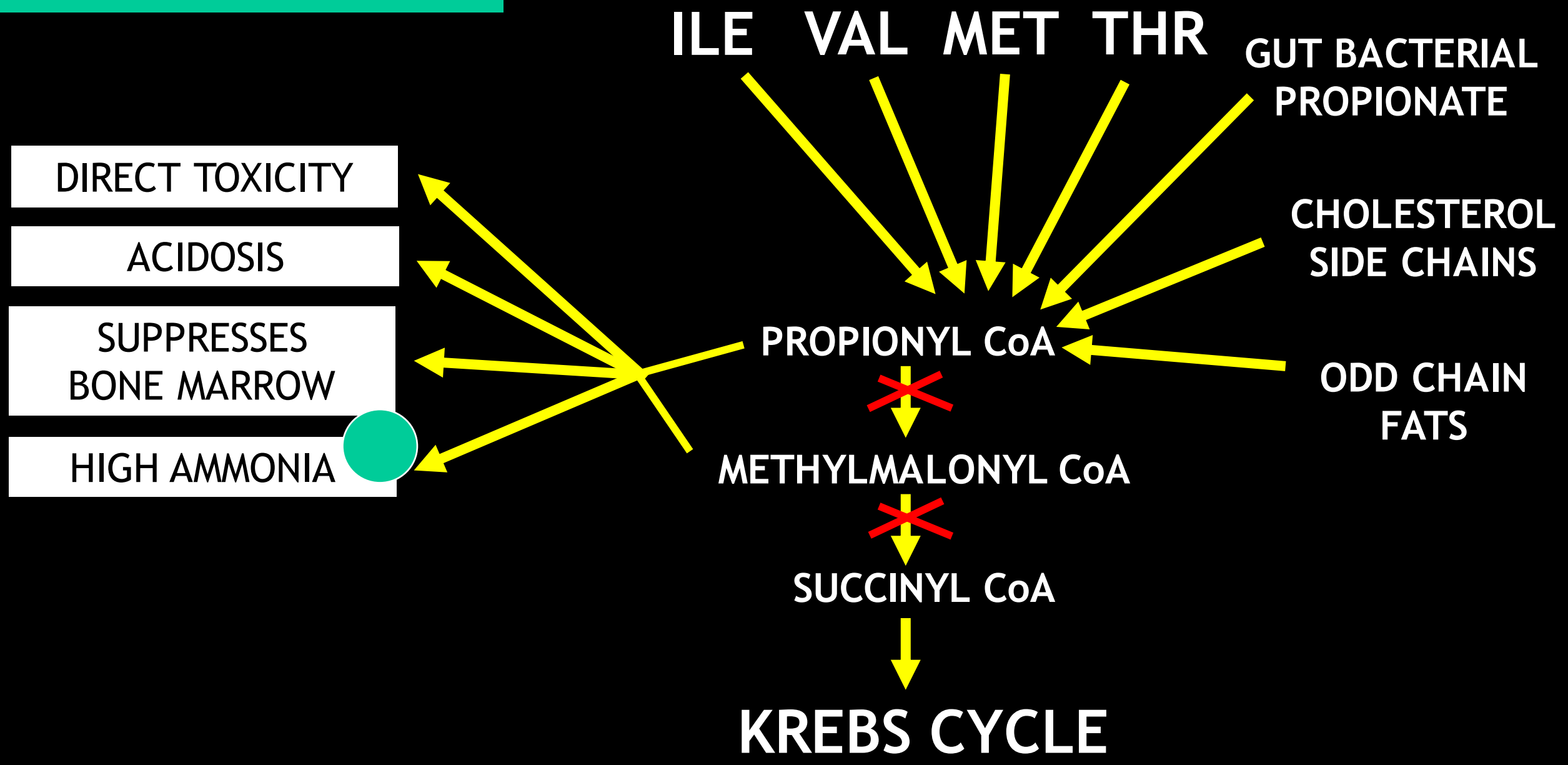
CHOLESTEROL SIDE CHAINS
ODD CHAIN FATS
DIRECT TOXICITY
ACIDOSIS
SUPPRESSES BONE MARROW
HIGH AMMONIA
PROPIONYL CoA
METHYLMALONYL CoA
SUCCINYL CoA
KREBS CYCLE

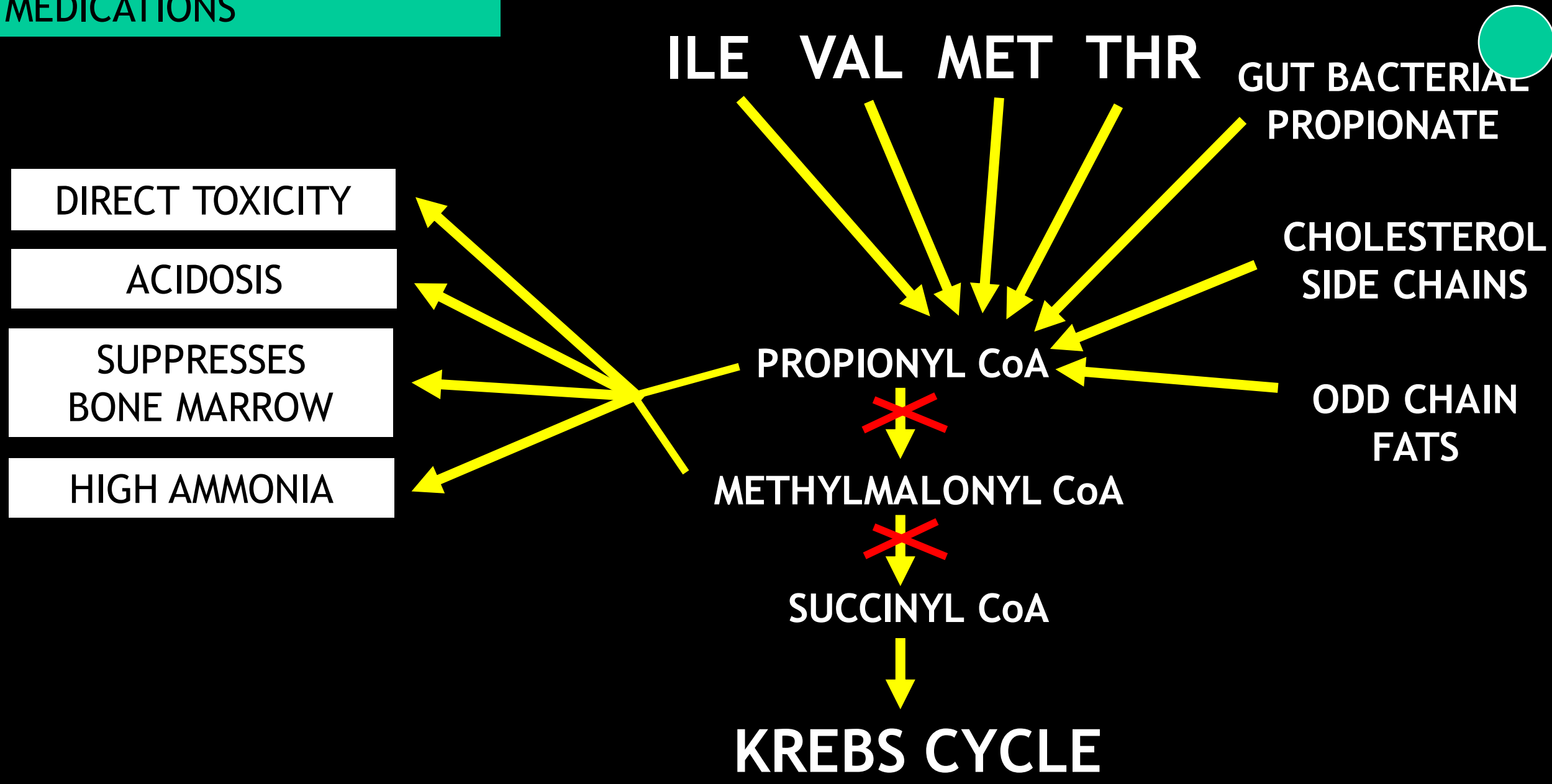
MONITORING/MEDICATIONS



MEDICATIONS



MEDICATIONS



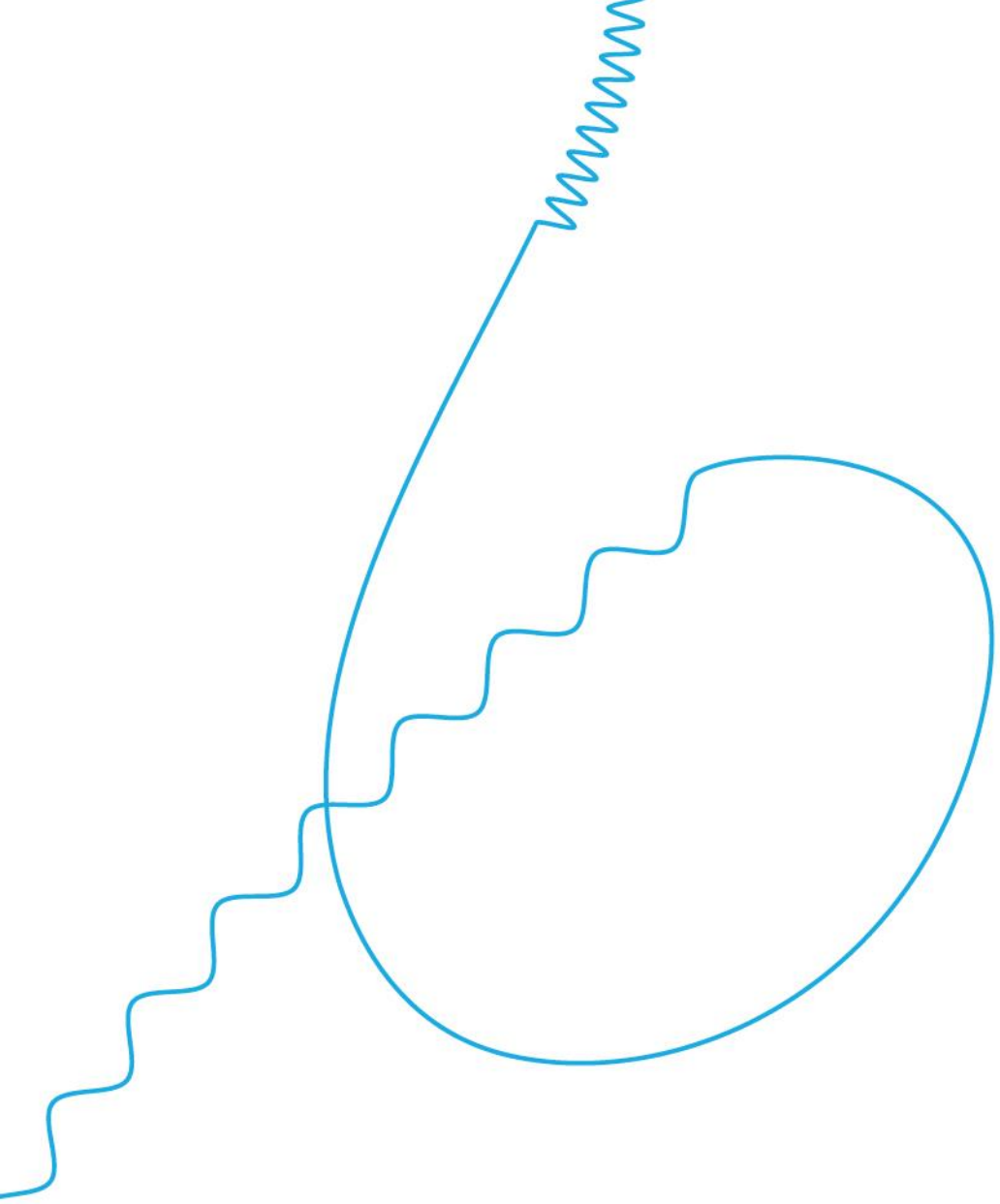
SO WE HAVE TREATMENTS FOR PA + MMA – YAY!

THIS TREATMENT PLAN IS UNSUSTAINABLE – BOO!

THIS TREATMENT PLAN IS UNSUSTAINABLE – BOO!

- These therapies address the symptoms; they don't address the underlying problem
- It's like playing "medical whack-a-mole"
- Patients and parents run ICUs at home
- Think PKU therapy "on steroids"

We need a therapy that can provide working enzyme…



Propionic Acidemia (PA)

Ruchira Glaser, M.D., M.S.

Senior Vice President, Therapeutic Area Head, Cardiovascular, Rare Diseases & Autoimmune

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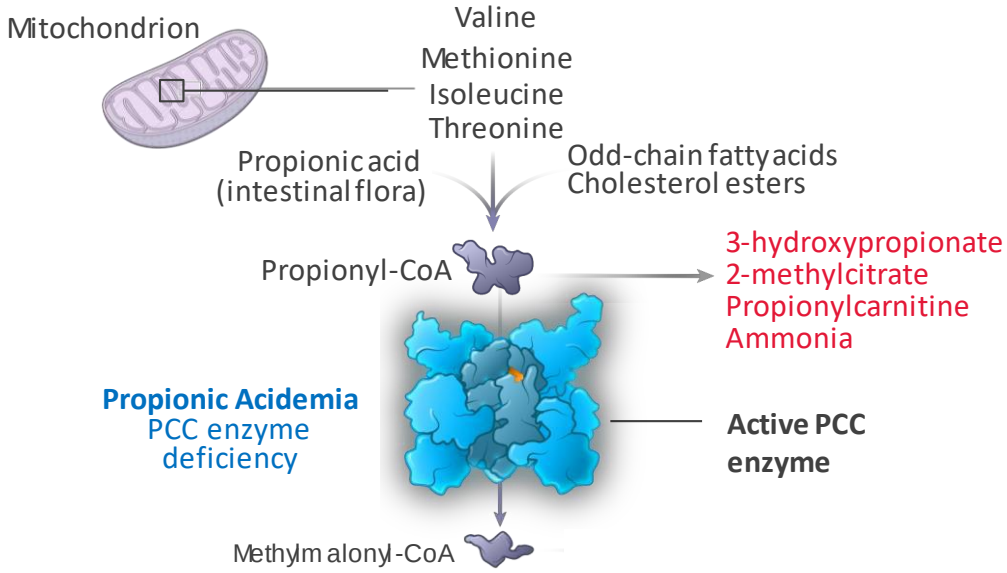
PA therapy (mRNA-3927) encodes for an intracellular enzyme

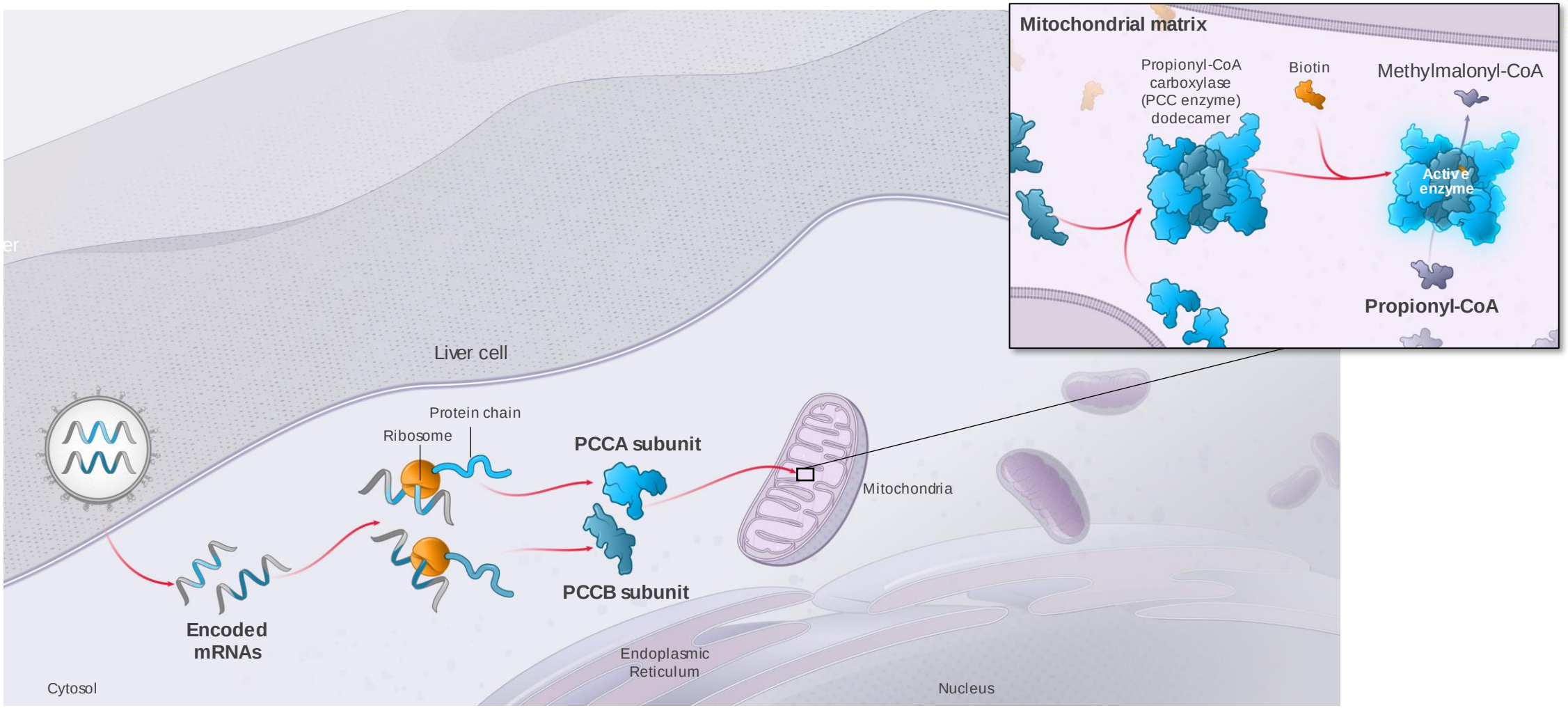
Moderna's mRNA therapy for PA (mRNA-3927) encodes for two proteins that form the deficient enzyme



PA biology

- **Changes in the *PCCA* and *PCCB* genes cause propionic acidemia**
  - These genes provide instructions for making two parts (subunits) of the propionyl-CoA carboxylase enzyme
  - Change in the *PCCA* or *PCCB* genes affect the normal function of the PCC enzyme and prevent the normal breakdown of propionyl-CoA
- As a result, propionyl-CoA and other **harmful compounds** accumulate causing acute **metabolic decompensation** events and **damage to the brain** and other organs, causing the serious health problems associated with propionic acidemia

mRNA-3927 encodes for PCCA and PCCB subunit proteins to form an active PCC enzyme



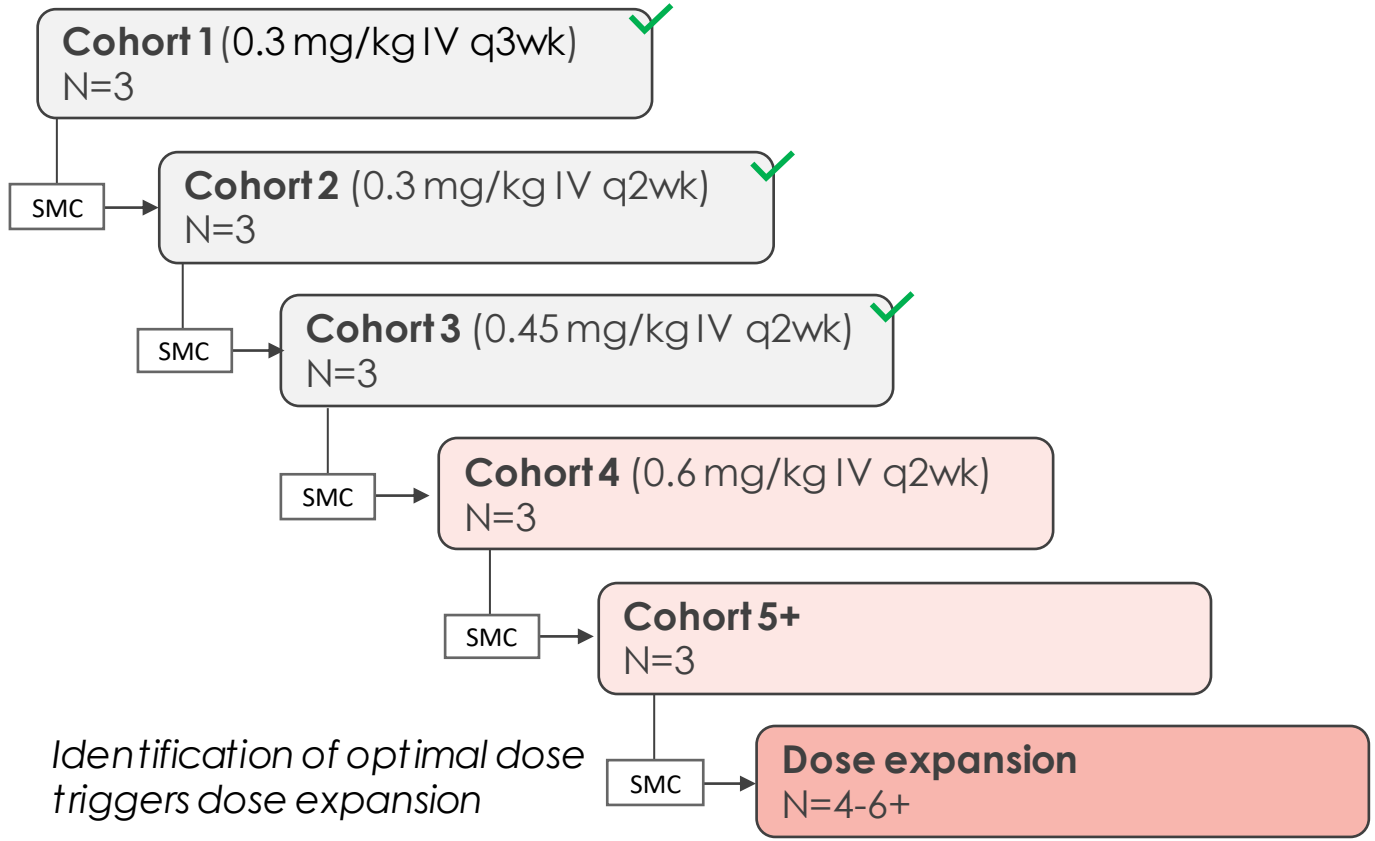
Ongoing Phase 1/2 Study designed to evaluate safety and pharmacology of mRNA-3927 in participants with PA

First study testing an mRNA therapeutic for intracellular protein replacement

- **Primary endpoints:** Safety and PK/PD
- **Secondary endpoints:** Incidence and severity of adverse events and change in plasma biomarkers (Hydroxypropionic acid (3-HP) and methylcitric acid (2-MC))
- **Exploratory clinical endpoints:** Metabolic decompensations events (MDE), cardiac function, quality of life

Phase 1/2 Trial Design

paramount study



SMC: Safety monitoring committee
✓ *: Fully enrolled*

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mRNA-3927: Summary of demographics and baseline characteristics

	Cohort 1 0.3 mg/kg q3W (n=4)	Cohort 2 0.3 mg/kg q2W (n=3)	Cohort 3 0.45 mg/kg q2W (n=3)	All (n=10)
Age at enrollment, median (years)	15.42	2.33	3.75	6.71
Min, Max	5.2 , 26.8	1.5 , 8.3	1.6, 15.3	1.5, 26.8
Age at disease onset, median (months)	0.0	0.0	0.0	0.0
Min, Max	0, 1	0, 0	0, 1	0, 1
Sex, n				
Male	2	0	2	4
Female	2	3	1	6
Race, n				
White	1	2	1	4
Black or African American	0	0	1	1
Asian	3	0	1	4
Other (Black African)	0	1	0	1
Ethnicity, n				
Not Hispanic or Latino	4	3	3	10
Weight				
Weight at baseline, median (kg)	44.40	15.80	18.00	23.05
Min, Max	21.6. 66.5	10.6, 24.8	11.2, 42.7	10.6, 66.5
Genotype				
PCCA	2	1	2	5
PCCB	2	2	1	5

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Overall Phase 1/ 2 clinical experience to date

- Ten participants dosed
- Three participants have >1 year of dosing
- 6 patient-years of experience on drug
- Over 120 intravenous doses administered
- Study is ongoing; independent safety monitoring committee approved moving to fourth cohort (0.6 mg/kg)
- All participants eligible have decided to continue on Open Label Extension (OLE) Study

Safety: Overall summary to date

- Generally well-tolerated to date
- No Dose Limiting Toxicities
- No Drug Related Serious Adverse Events
- No Discontinuations due to safety
- Only drug related adverse events were mild to moderate infusion related reactions (<10% of doses)

Safety: Summary of all adverse events measured

Adverse events (AEs) collected in the trial consist of treatment emergent adverse events (any AE reported after the start of dosing) and drug related AEs

	Cohort 1 0.30 mg/kg Q3W (N=4)	Cohort 2 0.30 mg/kg Q2W (N=3)	Cohort 3 0.45 mg/kg Q2W (N=3)	Total (N=10)
Treatment-emergent adverse events[1]	**3 (75.0)**	**3 (100)**	**3 (100)**	**9 (90.0)**
Dose Limiting Toxicity	0	0	0	**0**
AEs leading to study discontinuation	0	0	0	**0**
Serious adverse events[2]	2 (50.0)	2 (66.7)	1 (33.3)	**5 (50.0)**
Drug-related adverse events	**2 (50.0)**	**0**	**0**	**2 (20.0)**
Drug-related Serious Adverse Events	0	0	0	**0**

[1] Treatment-emergent adverse events are defined as AEs reported on or after the date that the intervention began
[2] Serious adverse events are defined as AEs including those leading to hospitalization, or disability, or are life-threatening or result in death, or deemed by the investigator as medically important, and include congenital anomaly or birth defect

Safety: Summary of serious adverse events

No drug-related SAEs; several SAEs due to underlying disease

	Cohort 1 0.30 mg/kg Q3W (N=4)	Cohort 2 0.30 mg/kg Q2W (N=3)	Cohort 3 0.45 mg/kg Q2W (N=3)	Total (N=10)
All Serious Adverse Events	**2 (50.0)**	**2 (66.7)**	**1 (33.3)**	**5 (50.0)**
Dyskinesia	0	1 (33.3)	0	1 (10.0)
Gastroenteritis viral	0	1 (33.3)	0	1 (10.0)
Mastoiditis	1 (25.0)	0	0	1 (10.0)
Parainfluenza virus infection	0	1 (33.3)	0	1 (10.0)
Poor venous access	0	0	1 (33.3)	1 (10.0)
Staphylococcal sepsis	1 (25.0)	0	0	1 (10.0)
Serious AEs related to underlying disease				
Metabolic disorder	1 (25.0)	0	0	1 (10.0)
Vomiting	1 (25.0)	0	1 (33.3)	2 (20.0)
Depression	1 (25.0)	0	0	1 (10.0)
Drug-related Serious adverse events	**0**	**0**	**0**	**0**

Treatment-emergent adverse events are defined as AEs reported on or after the date that the intervention began
All serious adverse events in the study were treatment-emergent adverse events

Safety: Summary of drug-related adverse events

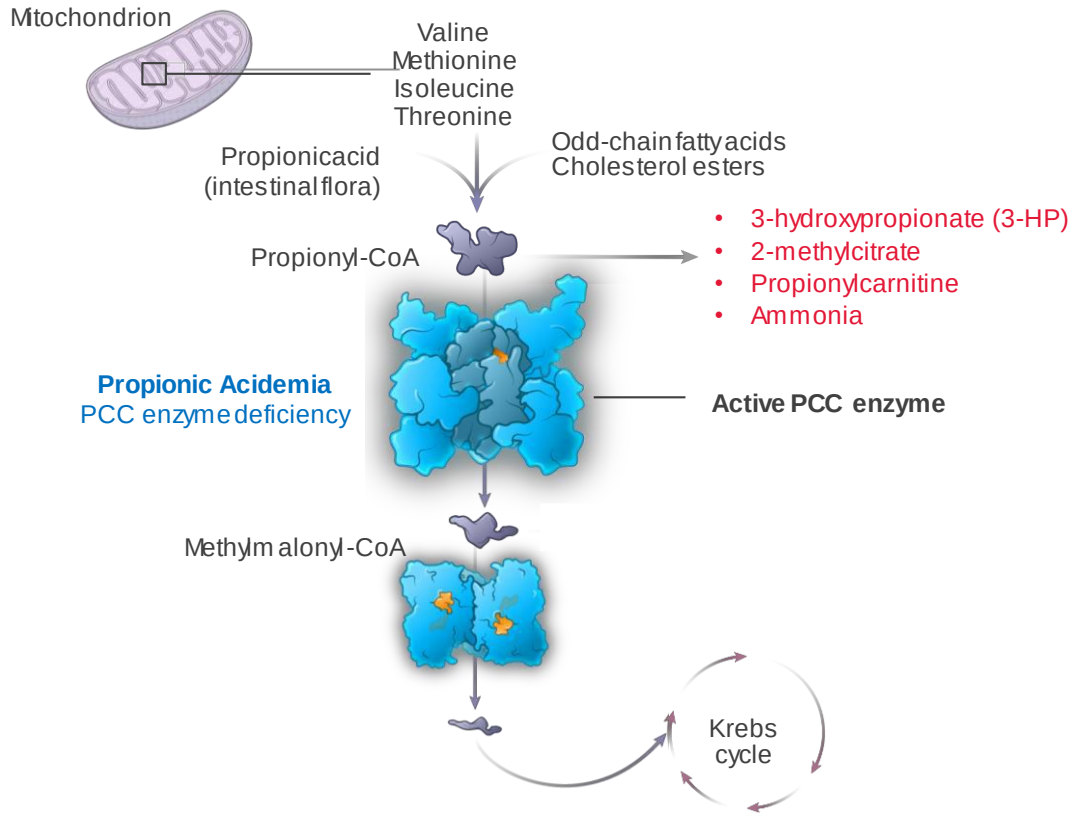
All drug related AEs were mild to moderate infusion related reactions (IRRs) that occurred in cohort 1 only

	Cohort 1 0.30 mg/kg Q3W (N=4)	Cohort 2 0.30 mg/kg Q2W (N=3)	Cohort 3 0.45 mg/kg Q2W (N=3)	Total (N=10)
Drug-related adverse events	**2 (50.0)**	**0**	**0**	**2 (20.0)**
By CTCAE grade				
Grade 1	2 (50.0)	0	0	**2 (20.0)**
Grade 2	1 (25.0)	0	0	**1 (10.0)**
Grade 3 or above	0	0	0	**0**
Serious adverse events	0	0	0	**0**
Total Number of Doses Given	61	49	12	**122**
Number of doses with IRRs	11 (18.0)	0	0	**11 (9.0)**

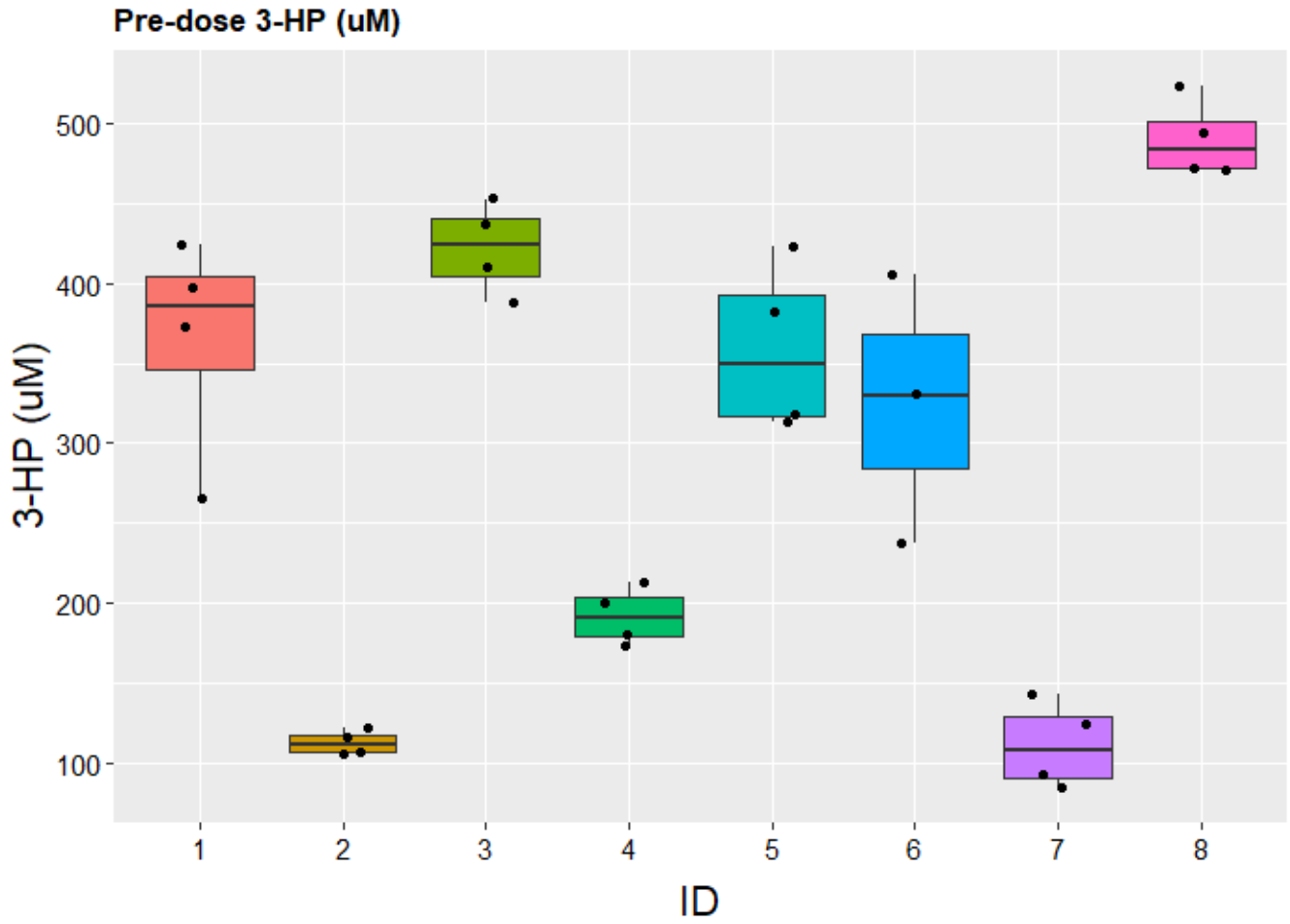
IRRs: Infusion-related reactions, defined as a drug-related AEs occurring within 24 hours of the start of a dose

Biomarkers to evaluate PK/PD of mRNA-3927

- While **several biomarkers have been described**, their pattern in individual patients over time and association with clinical events has not been thoroughly studied
- **No clinically validated** biomarkers
- We **explored 3-Hydroxypropionate (3-HP) as a potential biomarker**



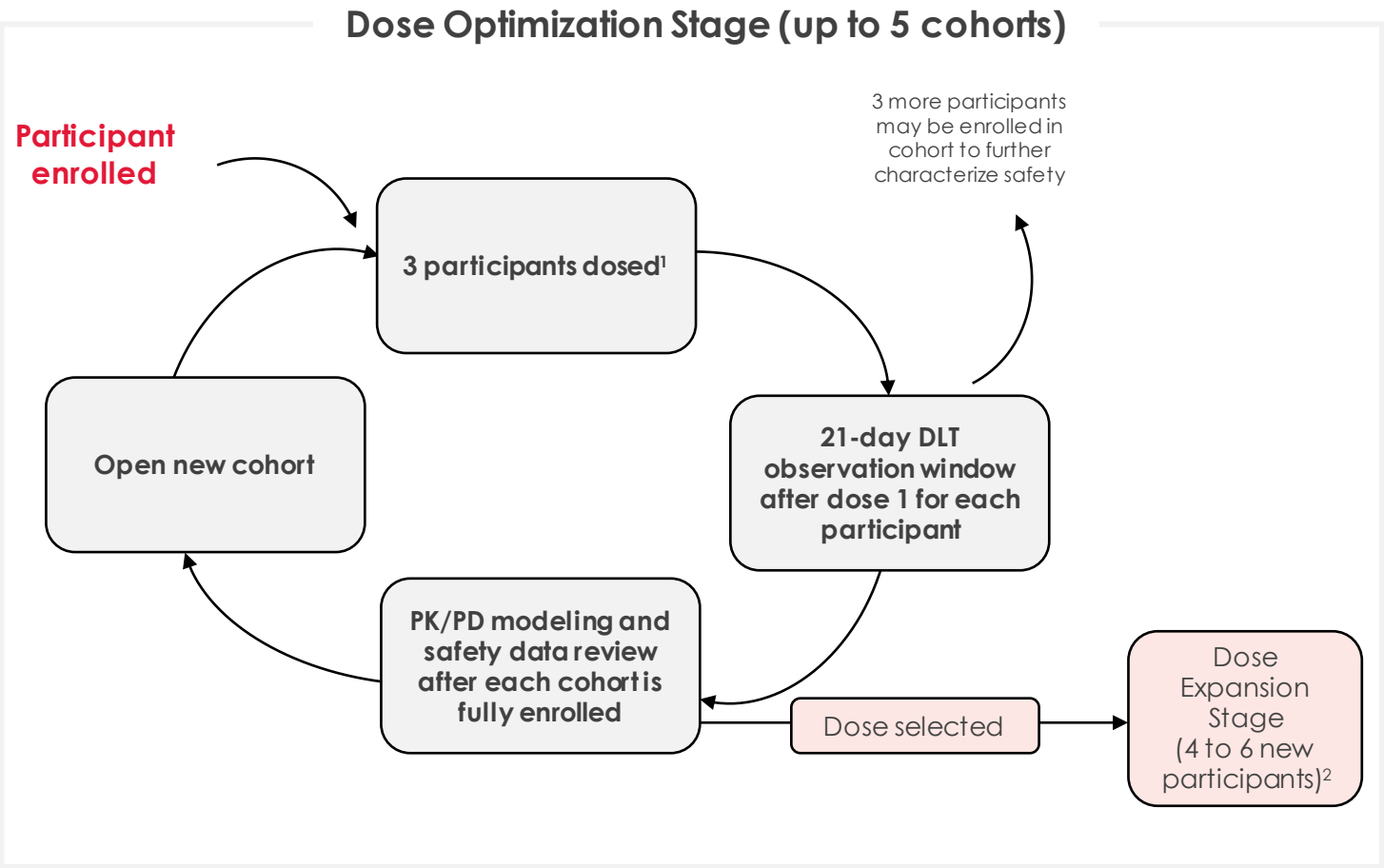
Baseline 3-HP biomarker levels highly variable across patients



PA genotype	Patient ID
PCCA	1, 5, 8
PCCB	2, 3, 4, 6, 7

- Each patient in the trial had four 3-HP values measured from blood draws taken before treatment
- Pre-treatment 3-HP values are highly variable between patients and within patients

Adaptive study design to identify optimal dose level and frequency



DLT = dose-limiting toxicity; PD = pharmacodynamic(s); PK – pharmacokinetic(s)
1. The first 2 participants will be ≥ 8 years of age
2. In the dose expansion stage, a minimum of 2 participants with each PA subtype will be enrolled

- Shorten interval from 3 weeks to 2 weeks (Cohort 2)
- Increased dose to 0.45 mg/kg (Cohort 3)
- Increased dose to 0.6 mg/kg (Cohort 4) expected to begin dosing shortly

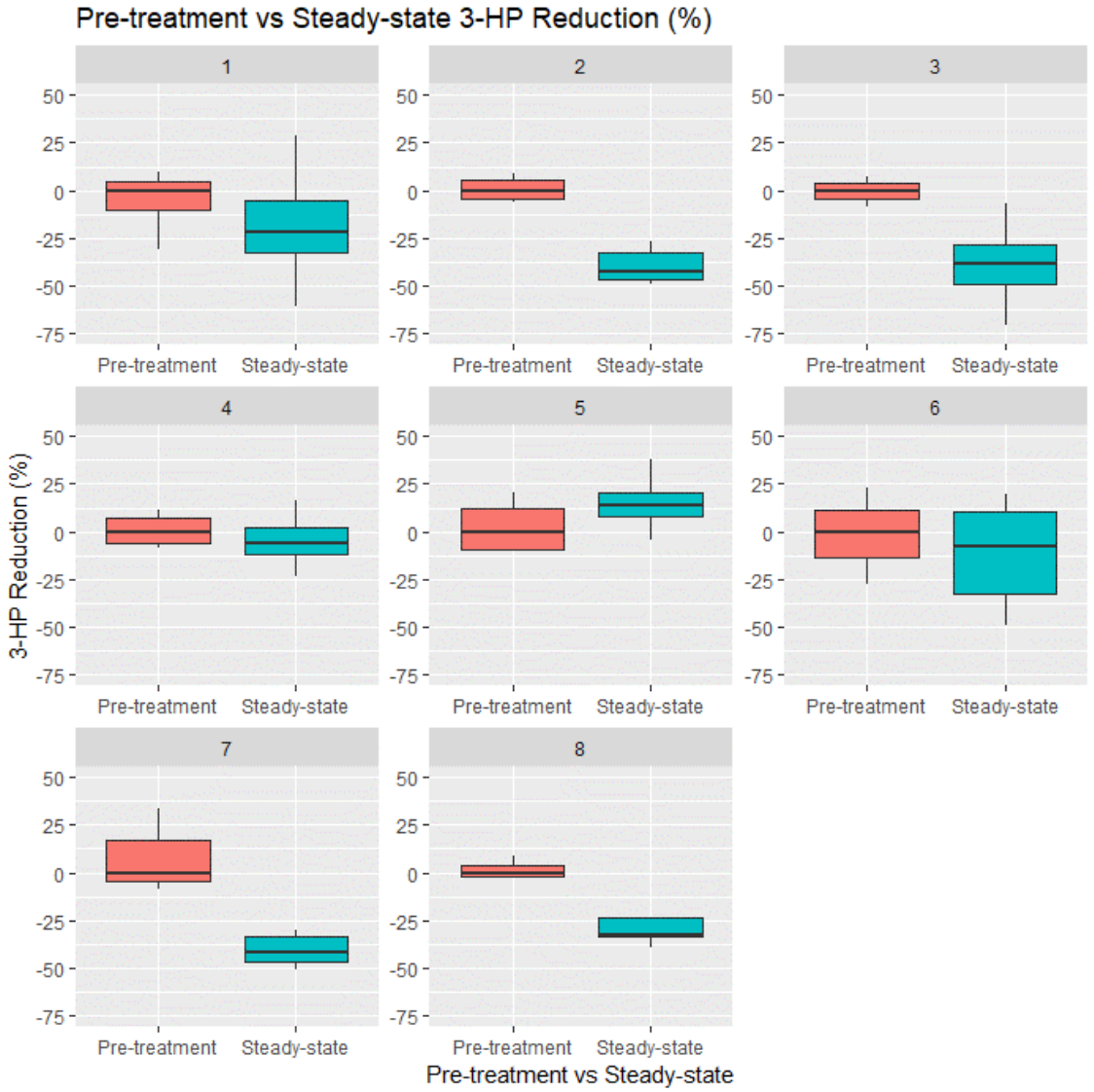
Significant reduction in 3-HP biomarker observed

- 7/8 patients showed a numerical reduction in 3-HP

Cohort 1 (0.3 mg/kg Q3W)

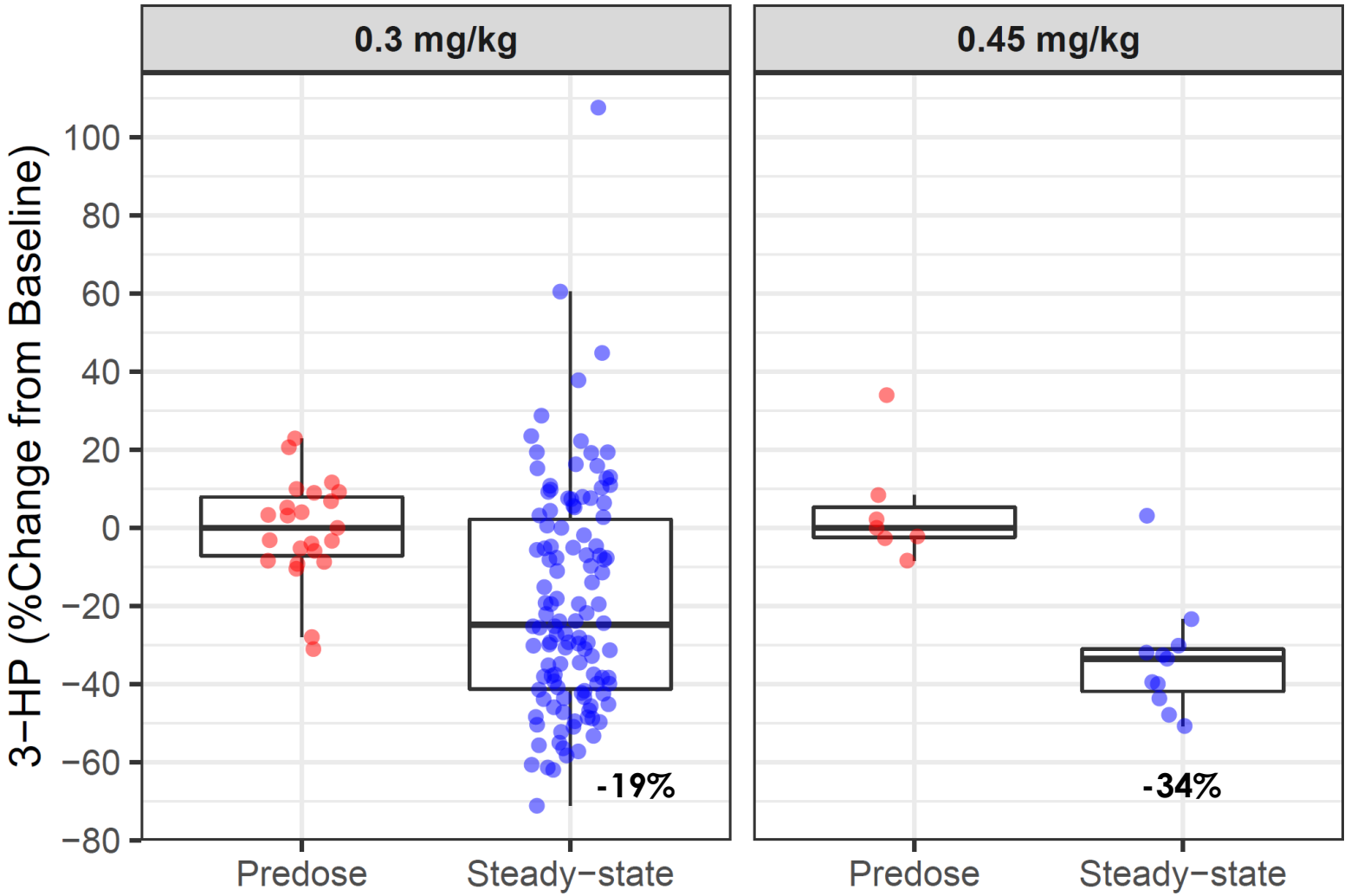
Cohort 2 (0.3 mg/kg Q2W)

Cohort 3 (0.45 mg/kg Q2W)



Steady-state = 3-HP measurements taken at all visits post 3rd dose

Encouraging trend in 3-HP biomarker



- Patients showed numerically lower 3-HP levels on treatment
- Trend suggestive of potential dose response with a greater decline from baseline at 0.45 mg/kg

Baseline= 3-HP measurements collected from pretreatment visits (N=4 visits/measurements per subject, prior to first dose);
Steady-state = 3-HP measurements taken at all visits post 3rd dose

Metabolic decompensation events are a potential primary endpoint

Protocol definition of MDE

- Exacerbation of symptoms of propionic acidemia: Persistent vomiting, anorexia/failure to feed, lethargy or increased seizure activity

and…

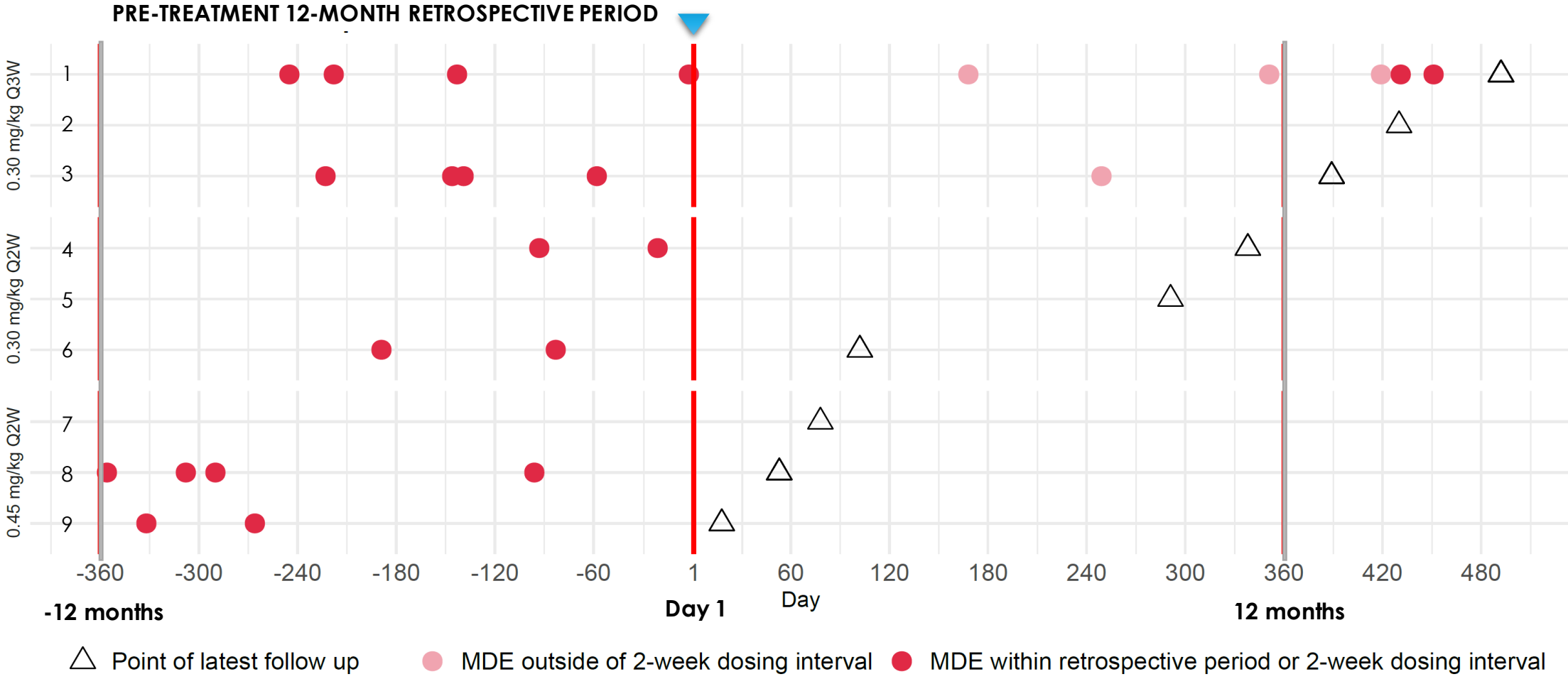
- Requiring emergency medicalcare (ER or hospitalization admission)

and at least one of:

- Metabolic acidosis (pH < 7.35) with high anion gap, or imminent metabolic acidosis with high anion gap (normal pH with reduced bicarbonate and/or PaCO2)
- Acute Hyperammonemia requiring intervention

Initial discussions with regulators supportive of MDE as primary endpoint for a pivotal study

Summary of metabolic decompensation events (MDEs)



Exposure duration of 3.8 years in participants with ≥1 retrospective MDE

- 48% Relative risk reduction in MDE frequency (p-value = 0.1817)
- No MDEs in two-week dosing interval cohorts

Summary of Phase 1/2 preliminary data; study ongoing to identify optimal dose

- **Expanding clinical experience:** 6 patient-years of experience on drug and all participants eligible have decided to continue drug on the Open Label Extension (OLE) Study
- **Safety:** Generally well-tolerated to date with no drug-related serious adverse events, no discontinuations due to safety and only mild-to-moderate infusion related reactions (<10% of doses)
- **Encouraging early trends in 3-HP biomarkers:** Suggestive of potential dose-dependent pharmacology
- **Clinical endpoints:** Encouraging data shows decrease in the number of metabolic decompensation events (MDEs)
- **Next steps**: Continue to enroll additional cohorts and escalate dose, identify optimal dose for expansion and continue to engage with regulators on registration path

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MMA (mRNA-3705) also ongoing in a Phase 1/2 study

Two cohorts are fully enrolled and we will have preliminary data by early 2023

landmark study

- Evaluating the safety and pharmacology of mRNA-3705 in patients 1 year of age and older with MMA in a multiple ascending dose study
- Secondary endpoints include incidence and severity of adverse events (AEs) and change in plasma biomarkers
- Recruiting patients in United Kingdom, Canada and US
- First two cohorts fully enrolled; study ongoing
  - Recently dosed third patient in 2nd cohort
- Preliminary data expected to be available by early 2023

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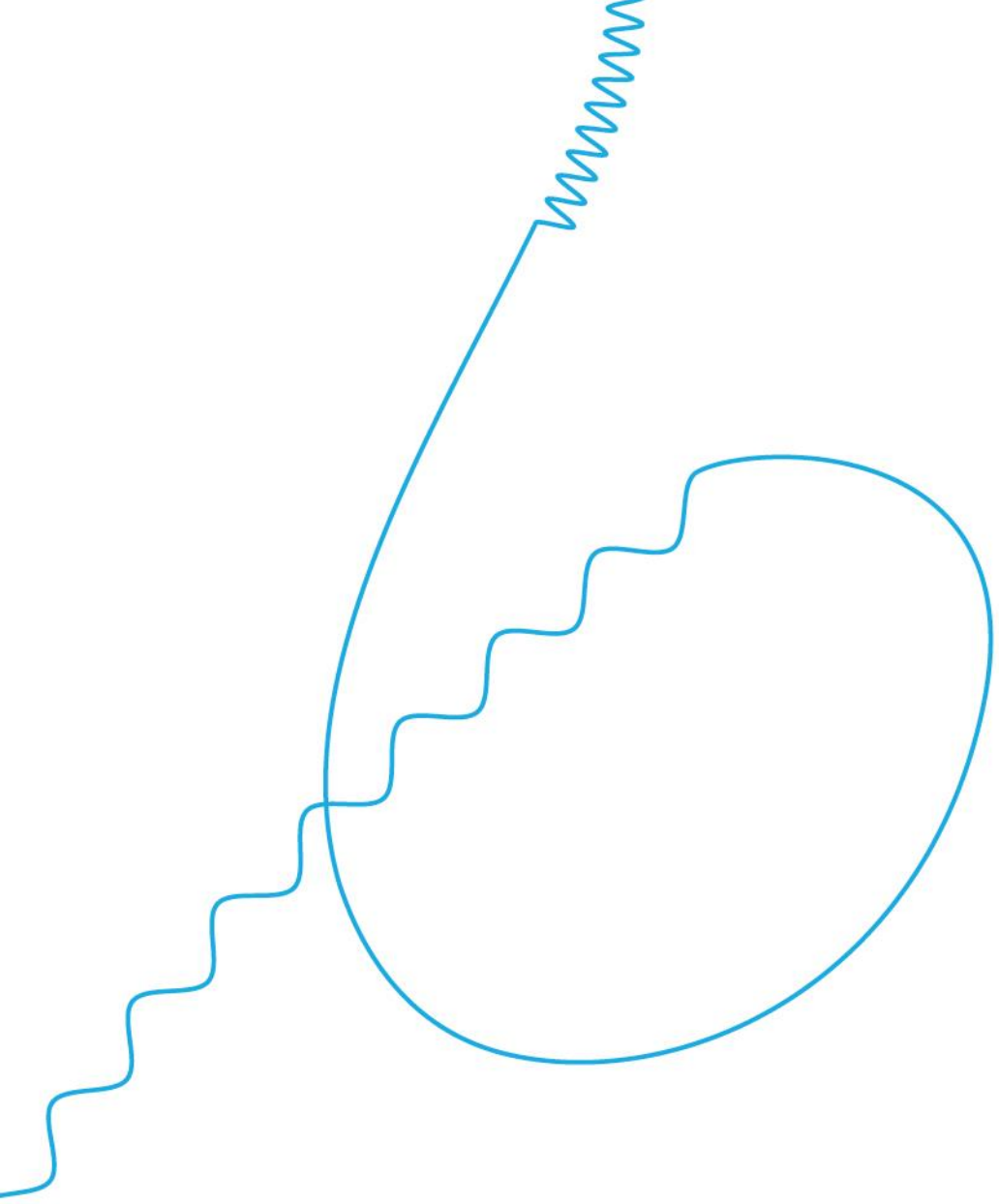

Glycogen storage disease type 1a (GSD1a)

Geoffrey Rezvani, M.D.

Executive Director, Program Leader (Cardiovascular and Emerging Therapeutics)

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Glycogen storage disease type 1a (GSD1a) overview

GSD1a refers to a rare inherited metabolic disease resulting from a deficiency in the metabolism of glucose

GSD1a biology

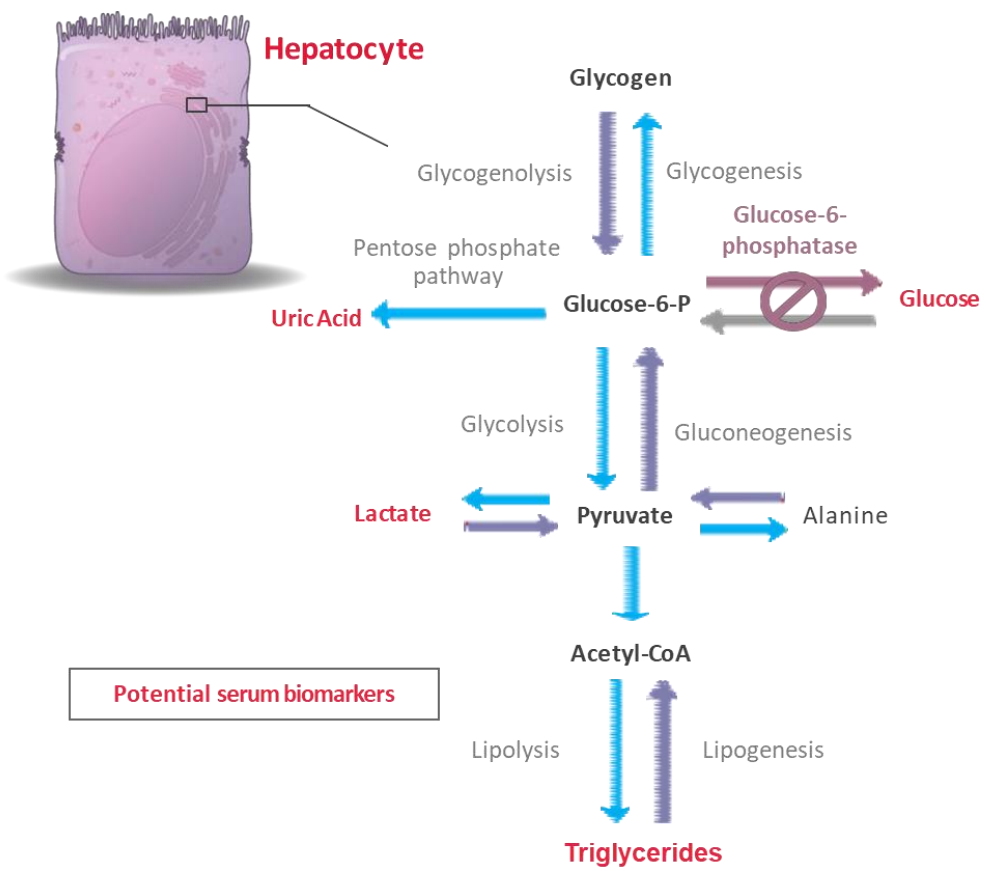
- GSD1a is caused by mutations within the enzyme glucose 6-phosphatase, G6Pase

Clinical manifestations

- **Life-threatening** hypoglycemia, long-term liver & kidney damage
- **Long-term hepatic complications are observed in 75% of adult patients** of which 10% are at risk of malignant transformation into hepatocellular carcinomas (HCC)

Glycogen storage disease type 1a (GSD1a) overview

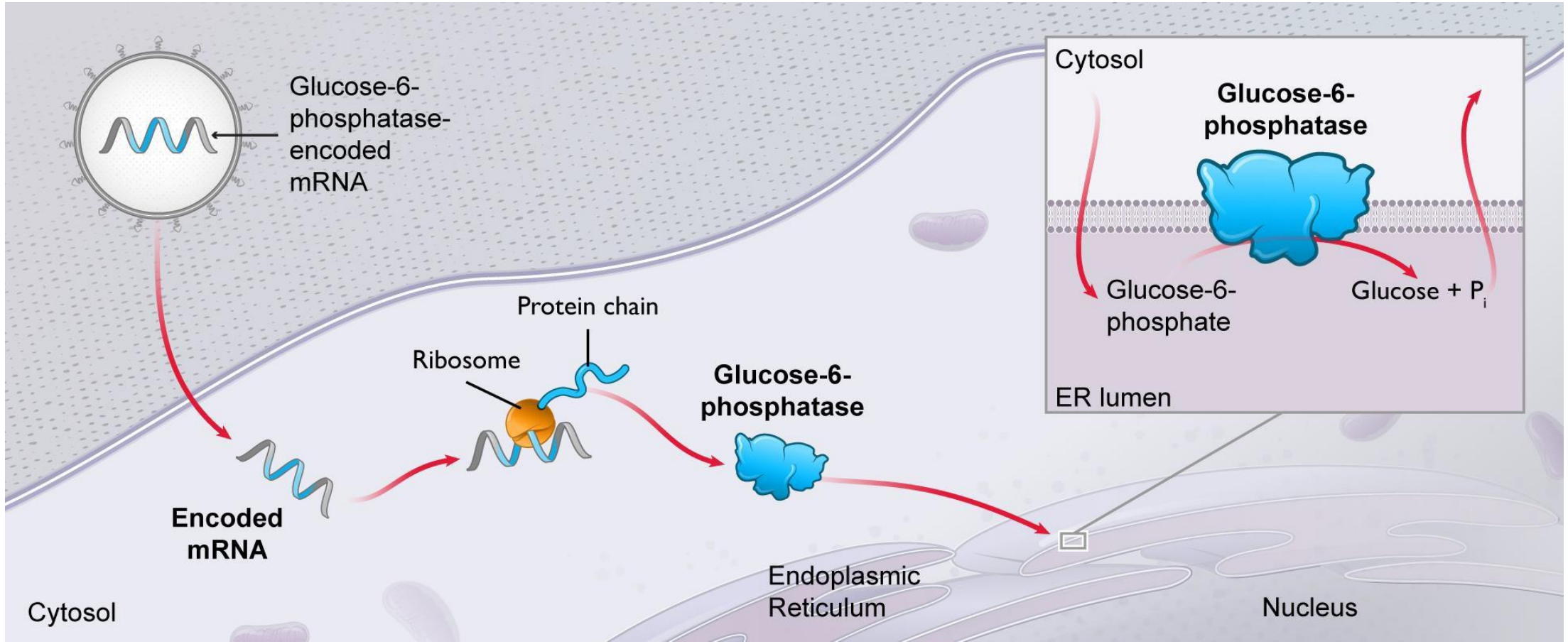
Significant unmet medical need



Standard of care

- **No approved therapy** for GSD1a
- Current interventions include:
  - **Strict diet control**; frequent consumption of uncooked cornstarch to improve hypoglycemia
  - Feedings by **gastric tube**
  - **Glycosade®** (cornstarch for dietary management)
  - **Liver/kidney transplantation**

GSD1a therapy (mRNA-3745) encodes for the G6Pase enzyme



Ongoing Phase 1 study of mRNA-3745 in GSD1a

Orphan Drug Designation granted by U.S. FDA

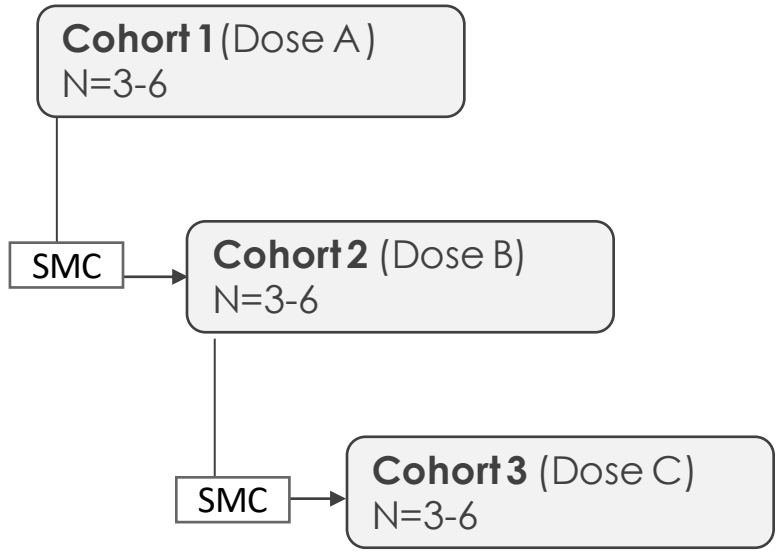
balance TRIAL

- Evaluate the **safety and pharmacology** of mRNA-3745 in patients 18 years of age and older with GSD1a

- **Single ascending dose study:** Challenging patients twice, on day 3 and day 8
  - **Biomarkers**: blood sugar and lactate
  - **Clinical**: improvement in fasting tolerance 3 days and 8 days after a single dose of mRNA-3745

- **Trial progress:** Enrollment ongoing (first participant dosed in June '22)

Phase 1 Trial Design



SMC: Safety monitoring committee

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Safe first-in-human administration of mRNA-3745

Intravenous infusion of mRNA-3745 with LNP2 without pre-medication was very well tolerated with only mild AEs

Patient 1

- Female, 21 years old
- GSD1a diagnosed at 6 months of age, managed with cornstarch
- Genotype: c.379_380dup (homo)

Patient 2

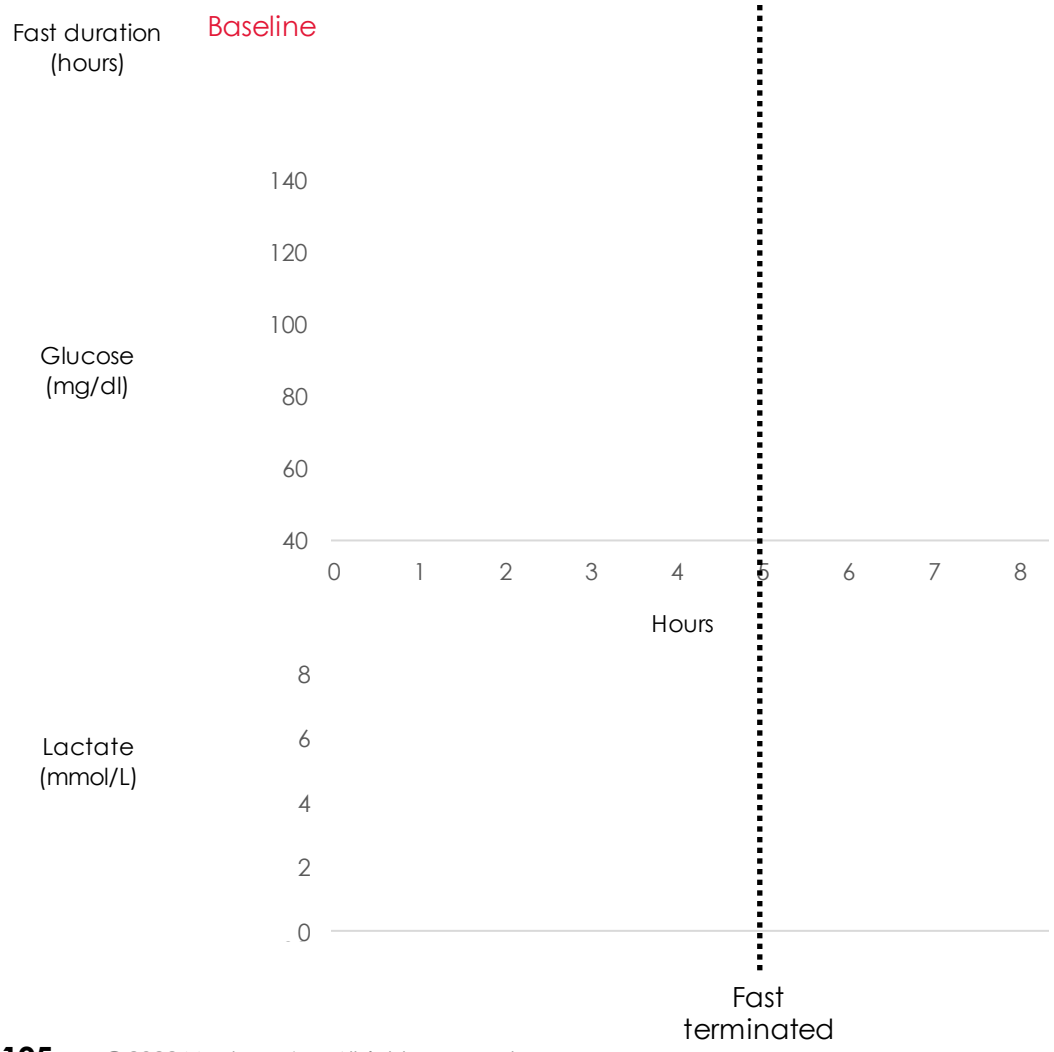
- Female, 18 years old
- GSD1a diagnosed at 2 years of age, managed with cornstarch
- Genotype: c.562G>C c.883C>T (compound het)

Safety

- No vital signs changes up to 12 hours post-infusion
- No serious adverse events
- No meaningful changes in safety labs, including hematology and liver function
- Follow up ongoing

Emerging efficacy data in GSD1a

Patient 1 (0.1 mg/kg)

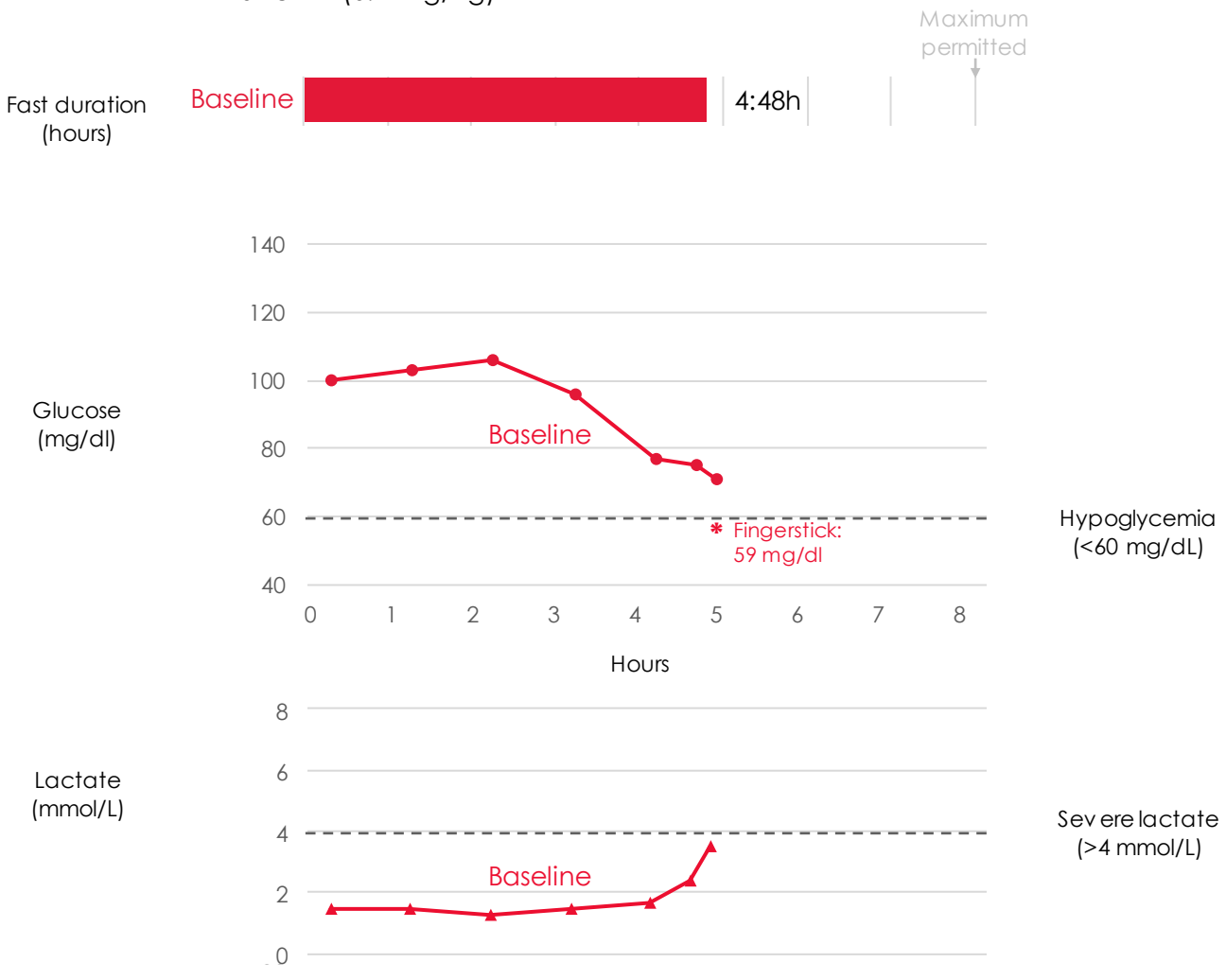


Fast terminated due to confirmed hypoglycemia after clinical symptoms

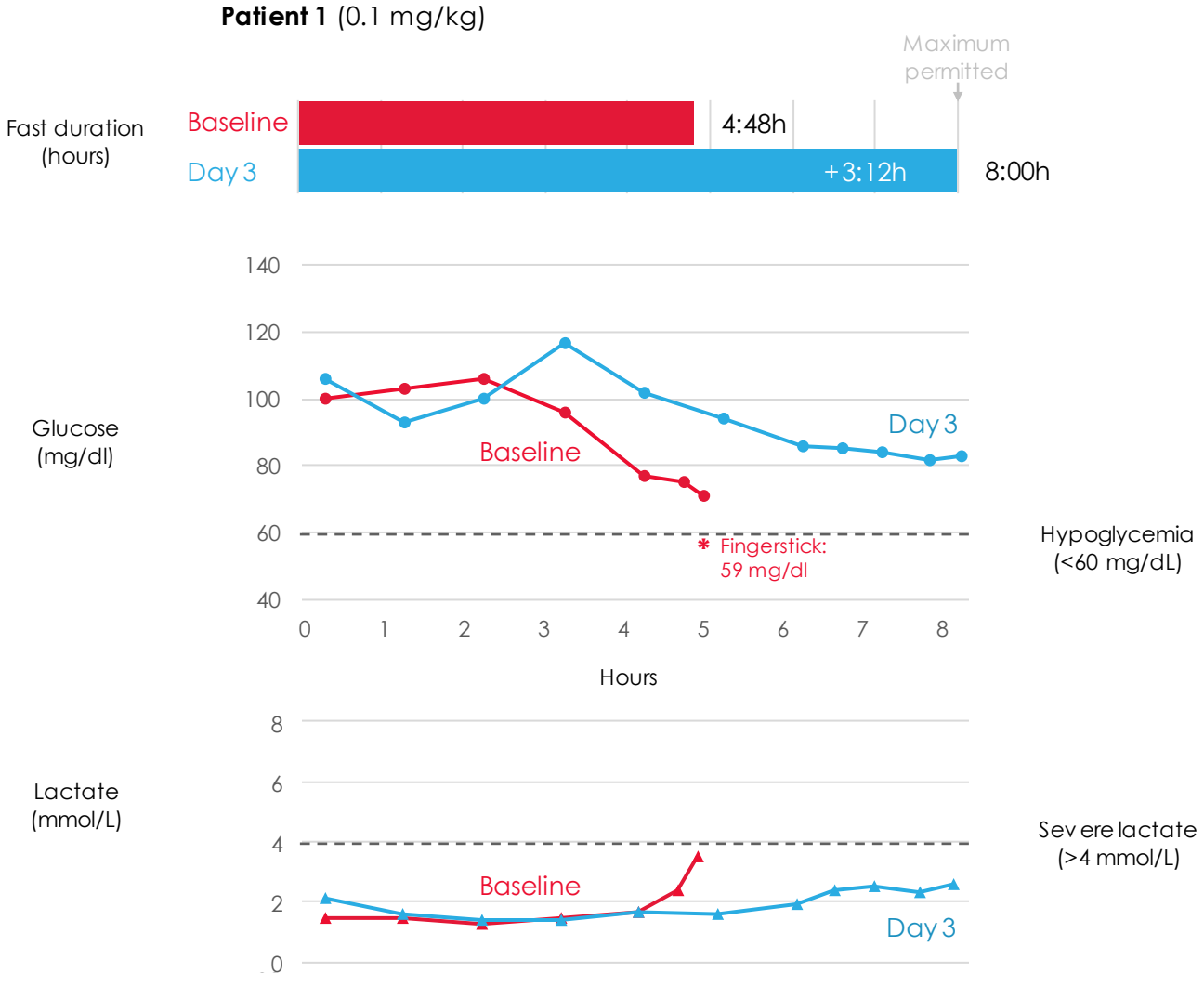
Evidence of severe metabolic strain with lactate approaching 4 mmol/L

Emerging efficacy data in GSD1a

Patient 1 (0.1 mg/kg)



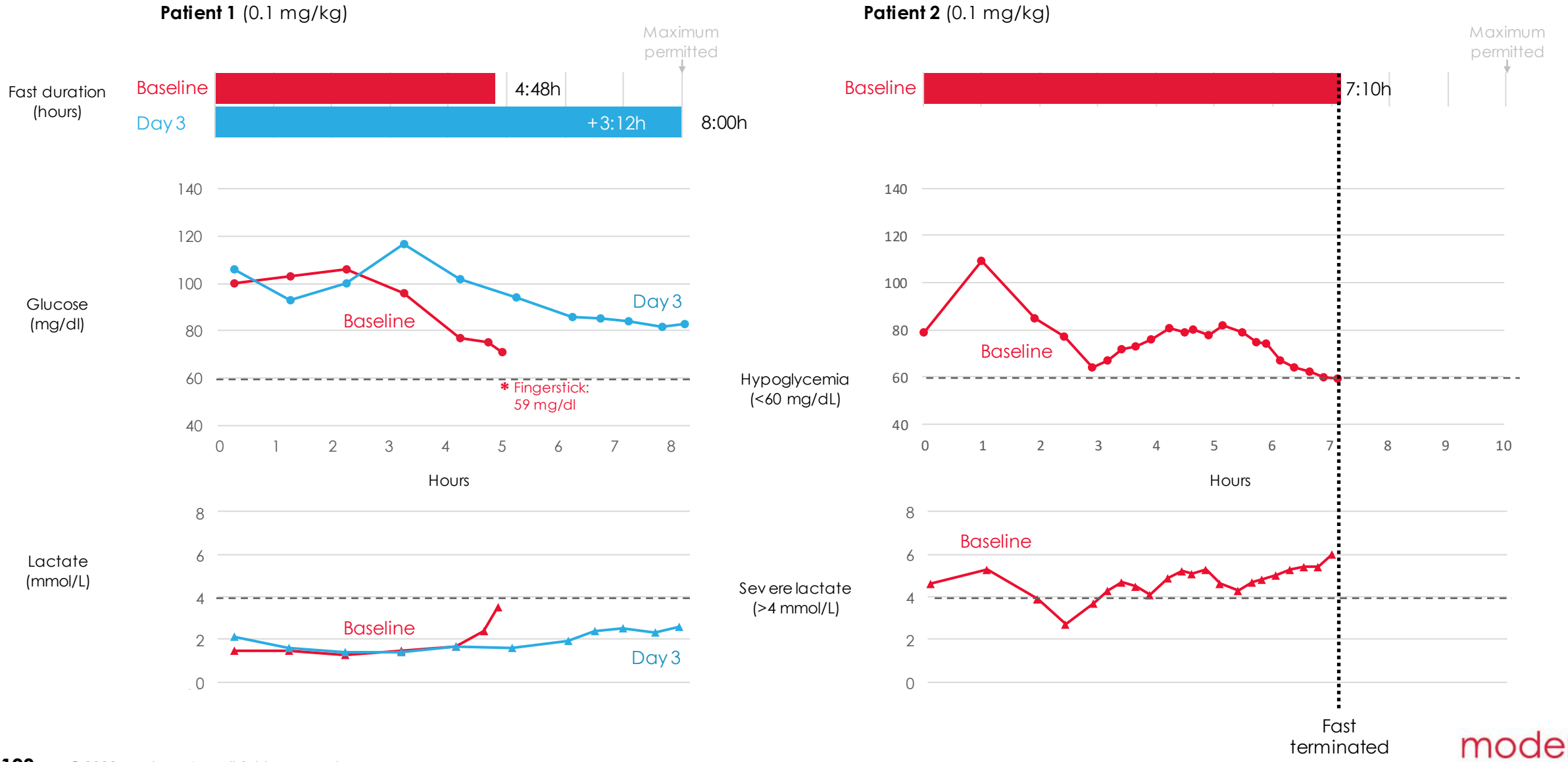
Emerging efficacy data in GSD1a



Patient able to complete full fast (limited to 8 hours)

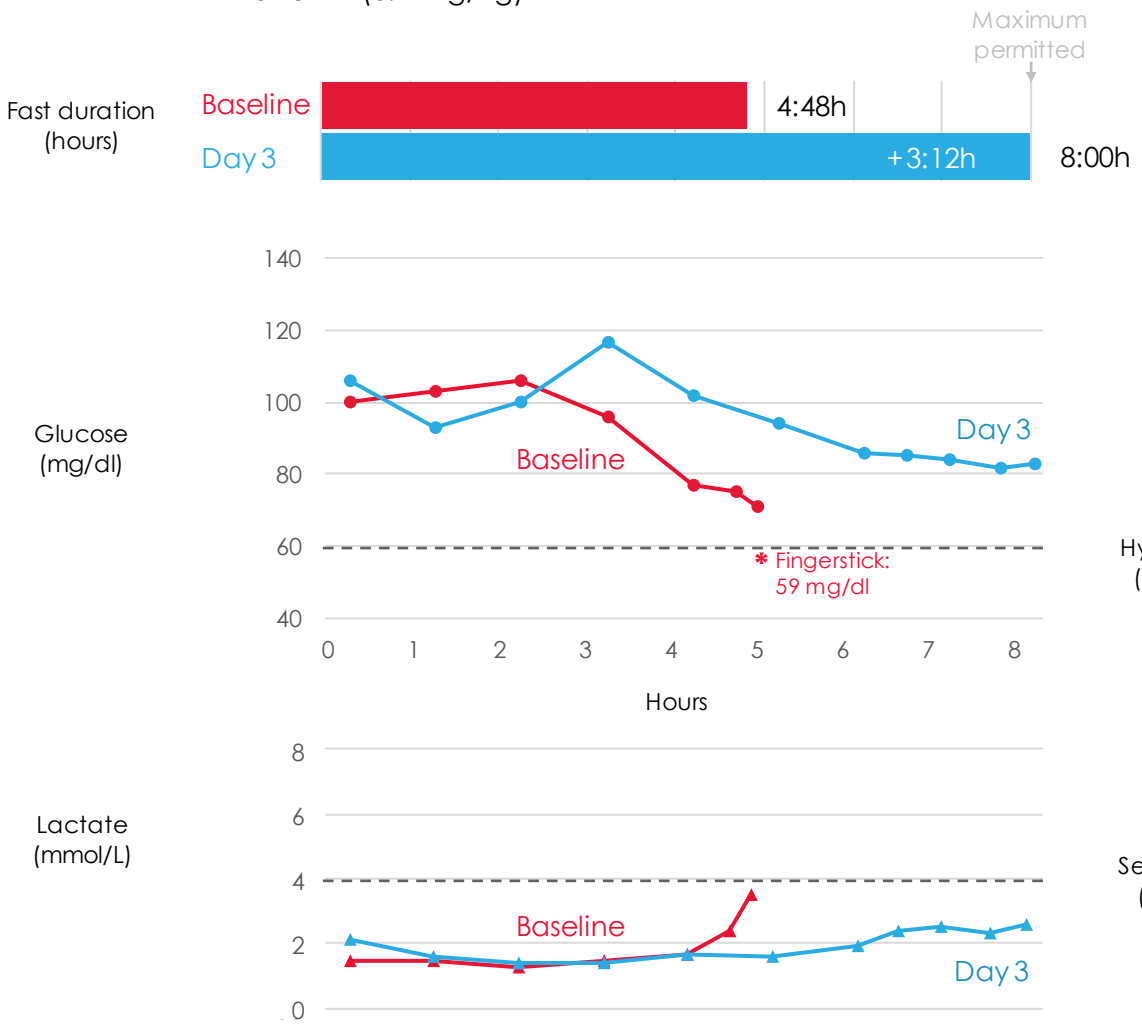
Glucose and lactate maintained throughout the fast

Emerging efficacy data in GSD1a

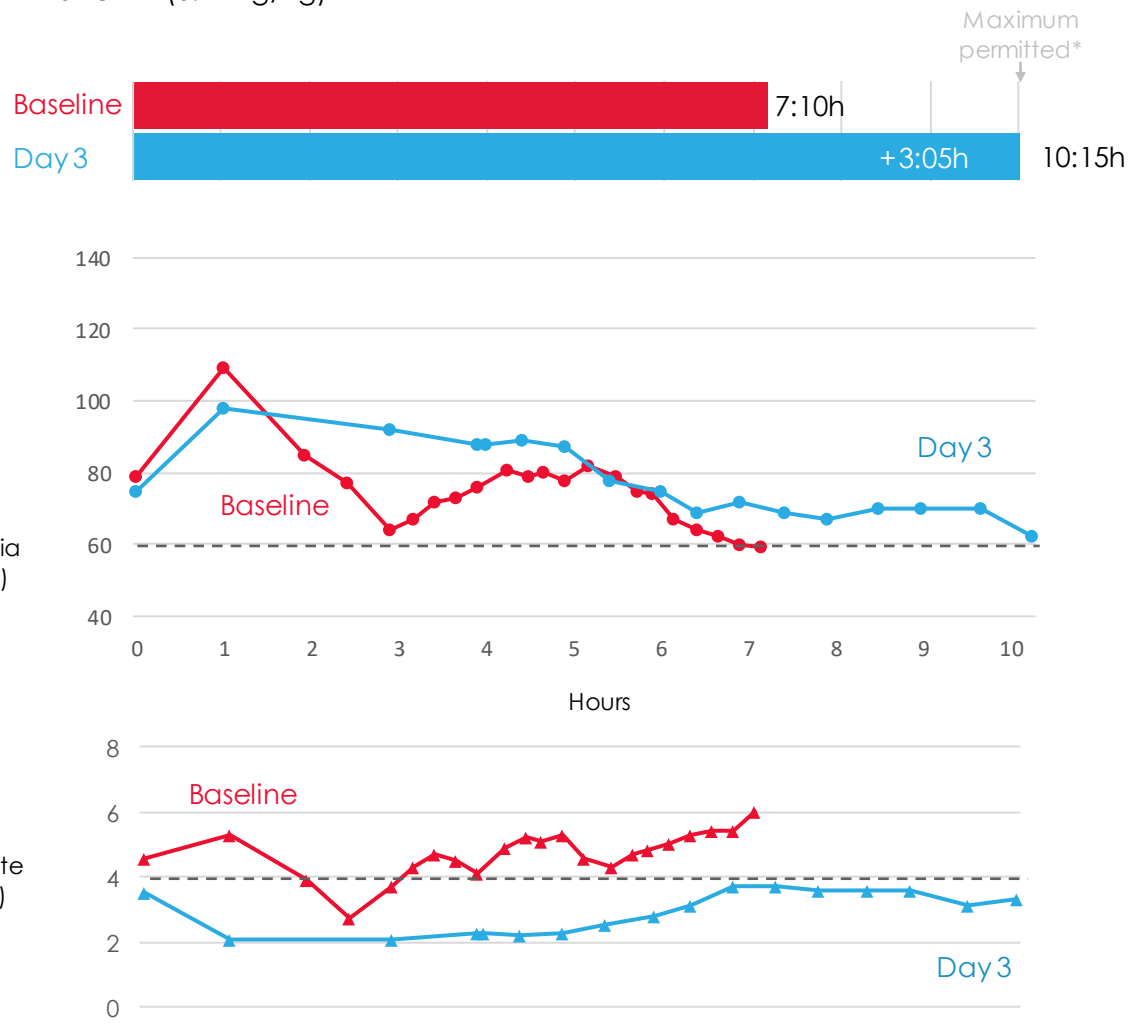


Emerging efficacy data in GSD1a

Patient 1 (0.1 mg/kg)

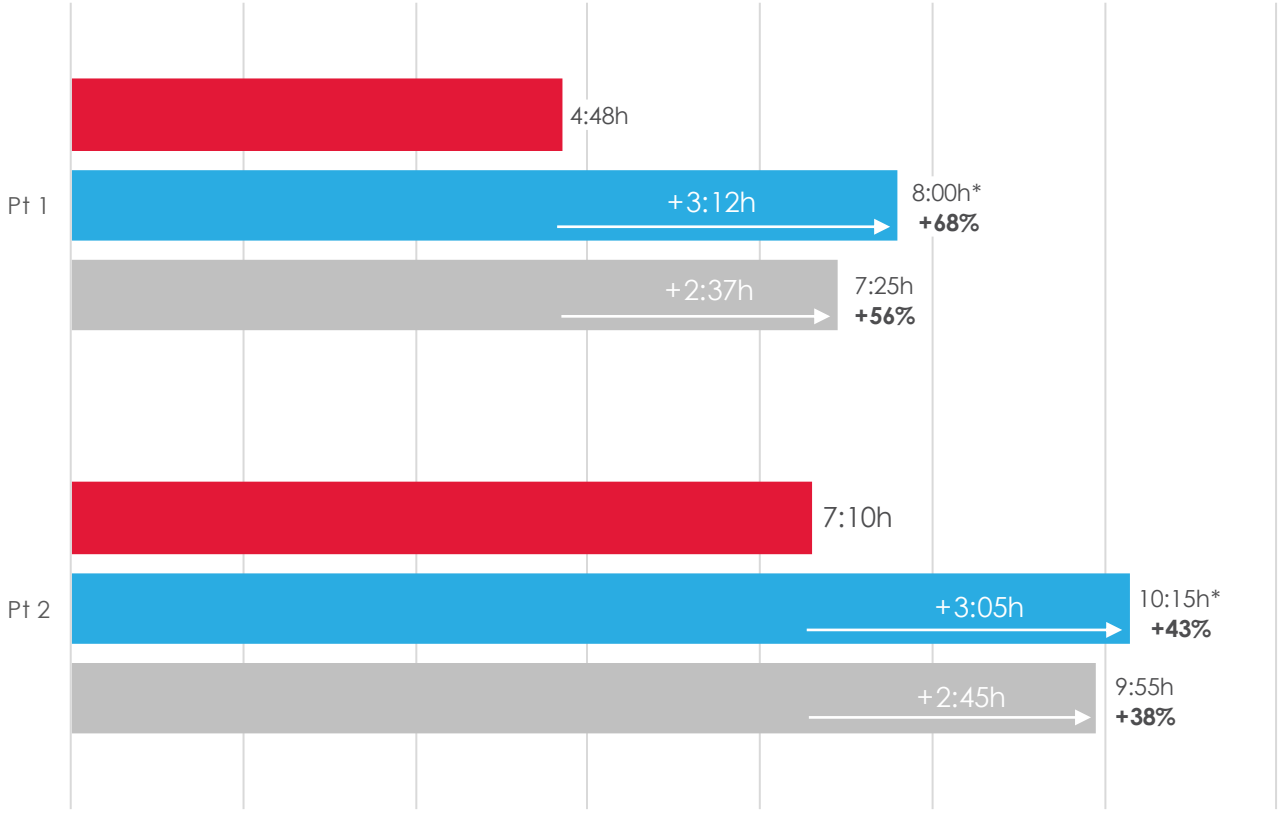


Patient 2 (0.1 mg/kg)



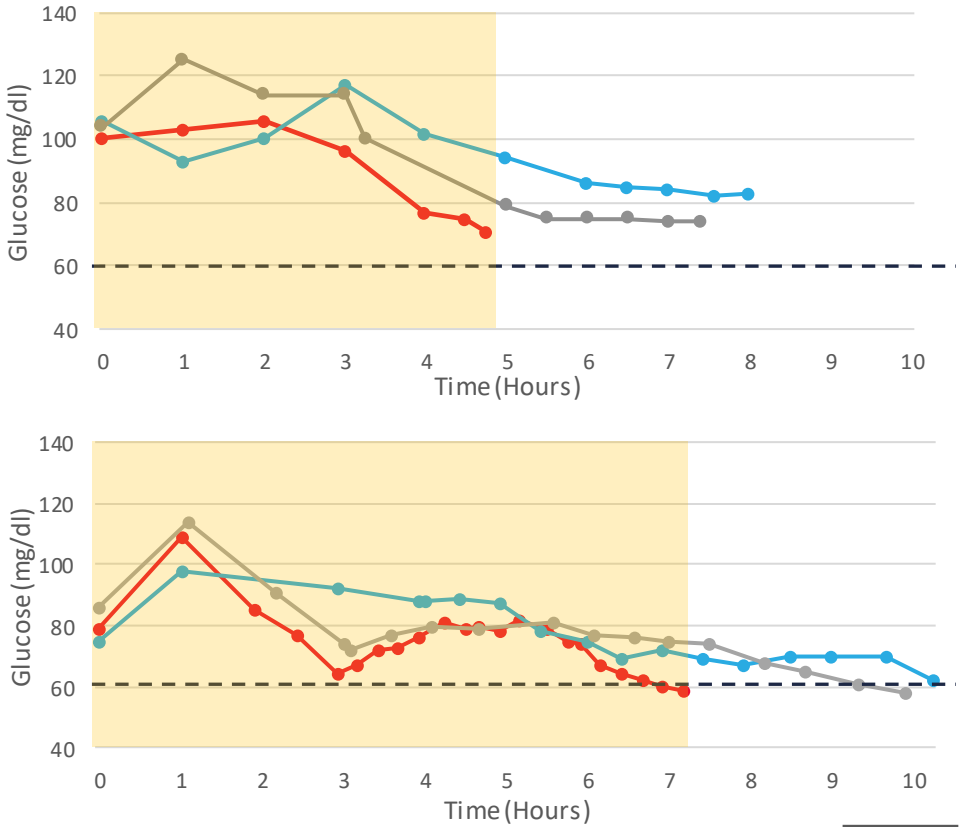
Improved fasting tolerance maintained through Day 8

Slight decrease vs. day 3, consistent with G6Pase enzyme half-life



Day -1
Day 3
Day 8

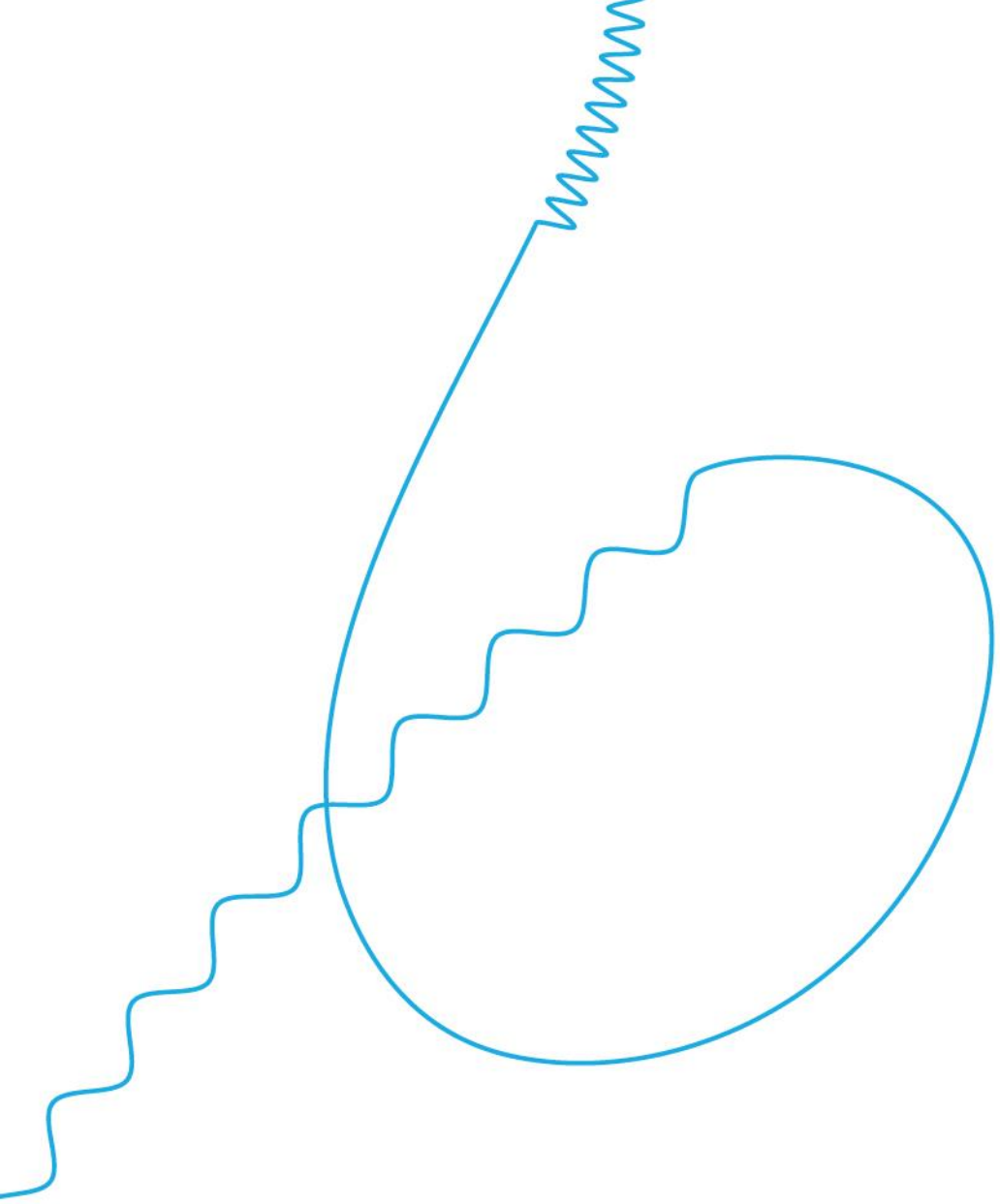
* Maximum Permitted



Day -1
Day 3
Day 8

mRNA-3745 for GSD1a – next steps

- Continue to **evaluate safety** of mRNA-3745 and LNP2
- **Assess fast tolerance** beyond day 8
- **Exploring higher doses** to extend potential repeat dose interval
- **Identify a dose** to move to repeat dose study



Personalized Cancer Vaccine (PCV) Review

Michelle Brown, M.D., Ph.D.

Executive Director, Program Leader, Oncology

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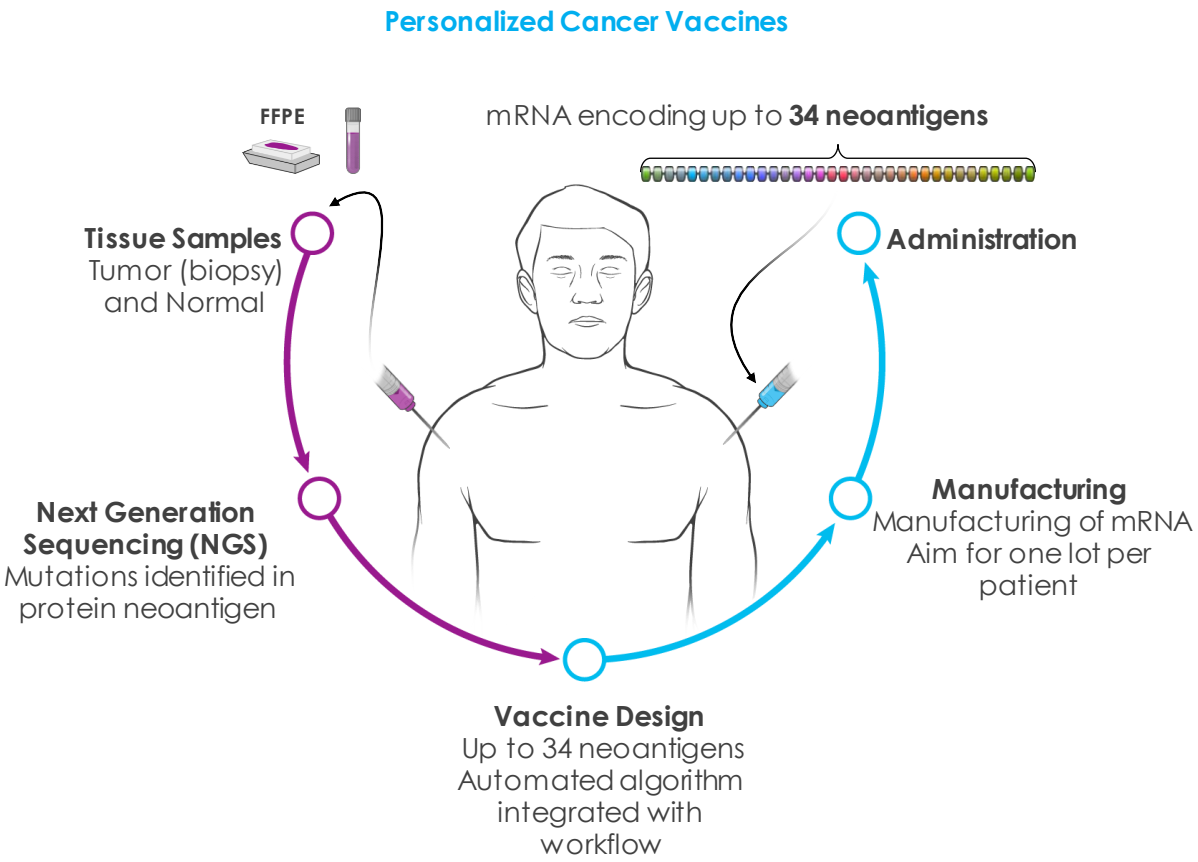
Personalized cancer vaccine (mRNA-4157)

Designed to target an individual patient's unique tumor mutations



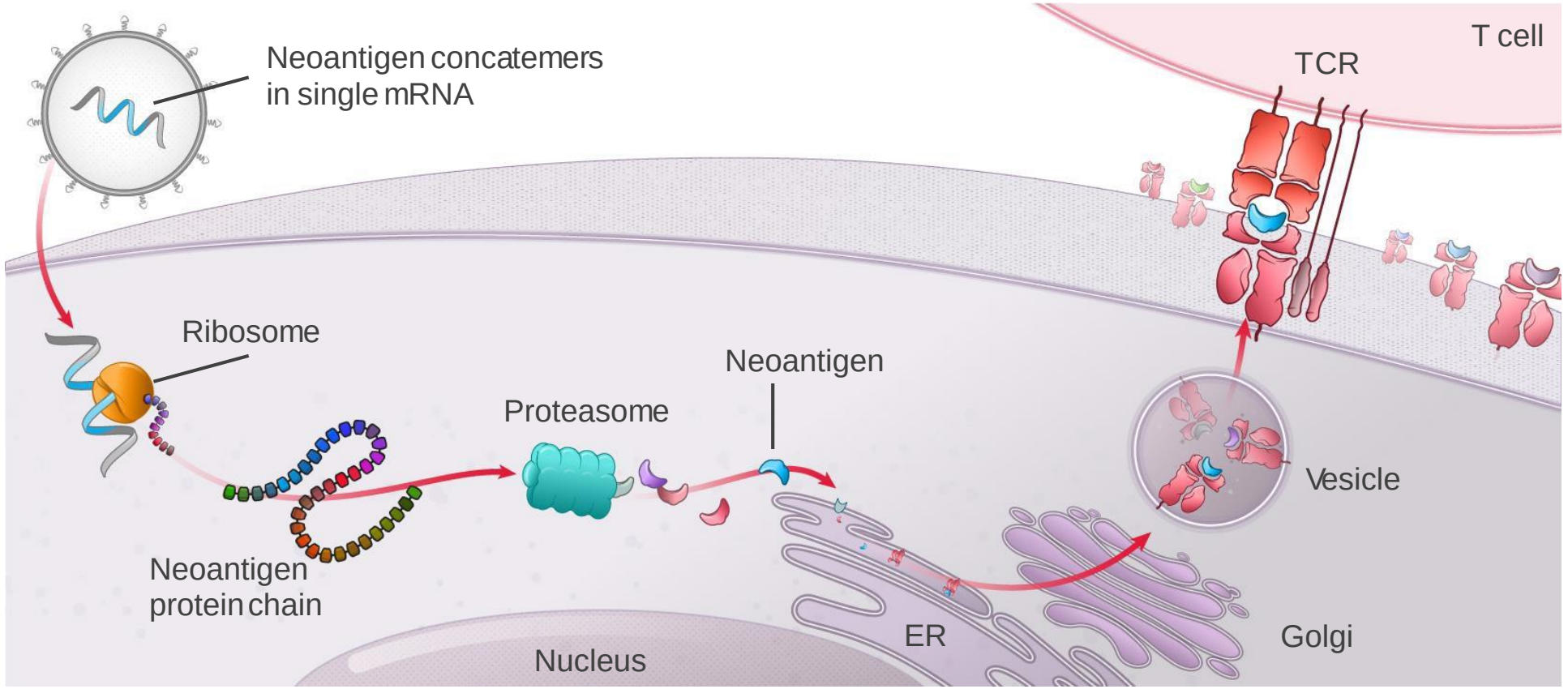
Personalized drug design

Rapid turnaround times

Needle-to-needle in just **weeks**

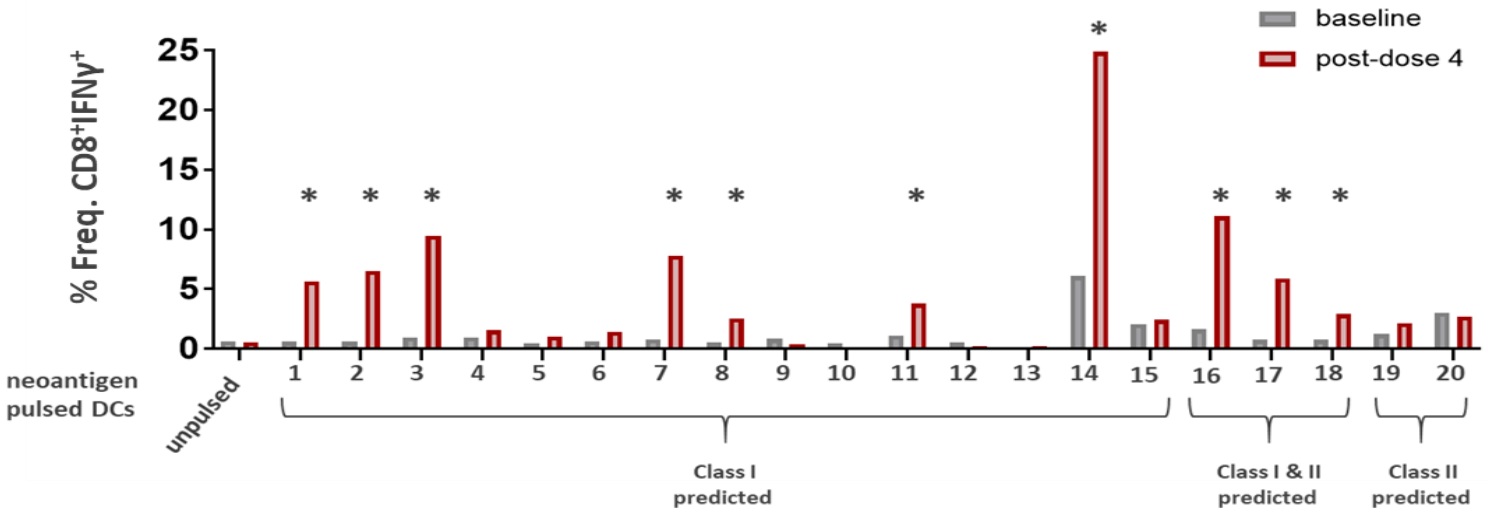
PCV vaccine (mRNA-4157) elicits T cells required for curative cancer therapy

Designed to target an individual patient's unique tumor mutations



Phase 1 study demonstrates PCV induces CD8 T-cell proliferation against selected neoantigens incorporated in vaccine

Previously shared at ASCO 2019



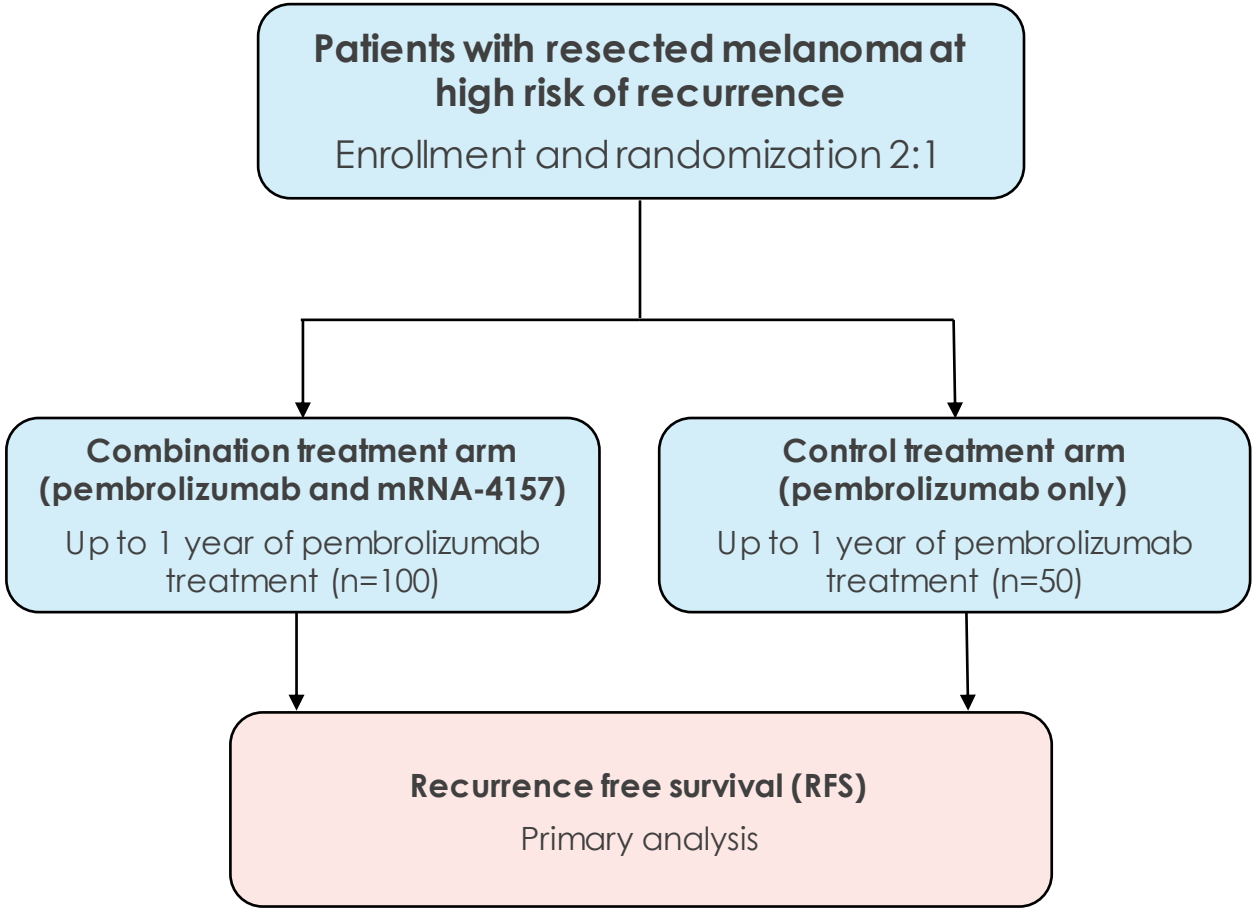
CD8 T cell responses to individual neoantigens were measured in in vitro stimulated (IVS, expanded) T cells
Flow cytometry plots show increases in % freq. of CD8 cells producing IFNγ 7d post 4th vaccine dose to multiple neoantigens
** Is greater than 3x increased in neoantigen specific CD8 T-cells post vaccination*

- **Greater than 3x increases in neoantigen specific CD8 T-cells were detected post 4th dose vaccination against 10 out of 18 class I targeted neoantigens**
- All positive CD8 T-cell responses post vaccination were to **neoantigens with high predicted binding affinity of < 500 nm**

Moderna 2019 ASCO presentation

PCV (mRNA-4157) is ongoing in a Phase 2 trial

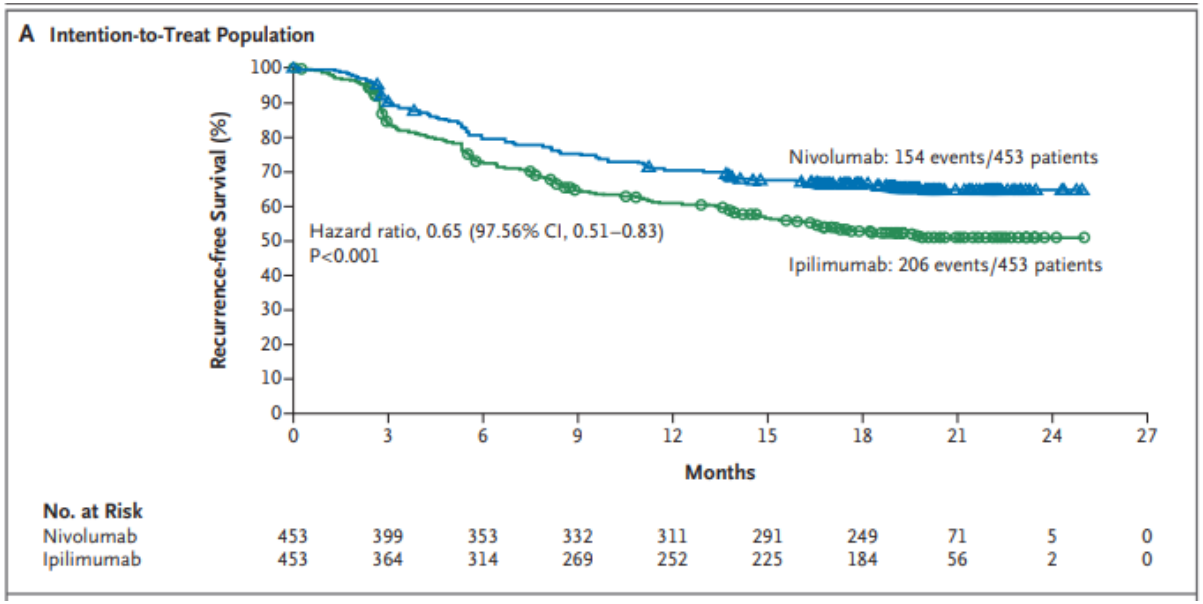
Primary endpoint is recurrence free survival compared to pembrolizumab



- Randomized, placebo controlled, PCV + pembrolizumab (KEYTRUDA®) vs. pembrolizumab alone (2:1)
- Resected melanoma patients - high recurrence risk
- Primary endpoint = recurrence free survival (RFS)
- Trial was fully enrolled (~150 participants) in September '21: Data expected in 4Q22

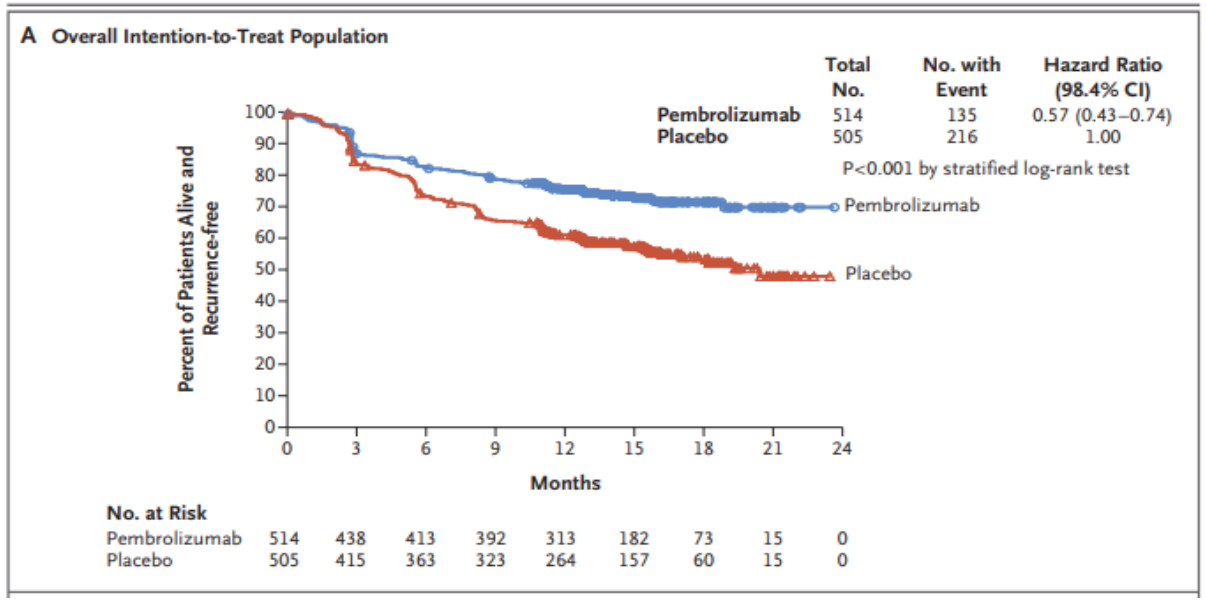
Previous studies in resected melanoma population: Kaplan-Meier curves for Checkmate-238 and Keynote-054

Checkmate-238 12mo RFS: 70.5% vs. 60.8%



Primary RFS analysis in the ITT Population

Keynote-054 12mo RFS: 75.4% vs 61.0%

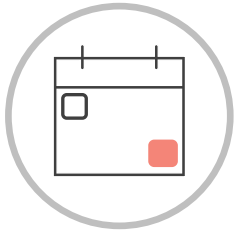


Primary RFS analysis in the ITT Population

1. Checkmate-238:A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects Who Are at High Risk for Recurrence Weber, Jeffery et al., The New England Journal of Medicine (2017), https://www.nejm.org/doi/full/10.1056/nejmoa1709030
2. Keynote 054: Adjuvant Immunotherapy With Anti-PD-1 Monoclonal Antibody Pembrolizumab (MK-3475) Versus Placebo After Complete Resection of High-risk Stage III Melanoma: A Randomized, Double- Blind Phase Trial of the EORTC Melanoma Group. Eggermont, Alexander et al., The New England Journal of Medicine (2018), https://doi.org/10.1056/NEJMoa1802357

Personalized cancer vaccine (PCV) summary

- **Primary endpoint analysis is RFS**; PCV + pembrolizumab vs. pembrolizumab alone

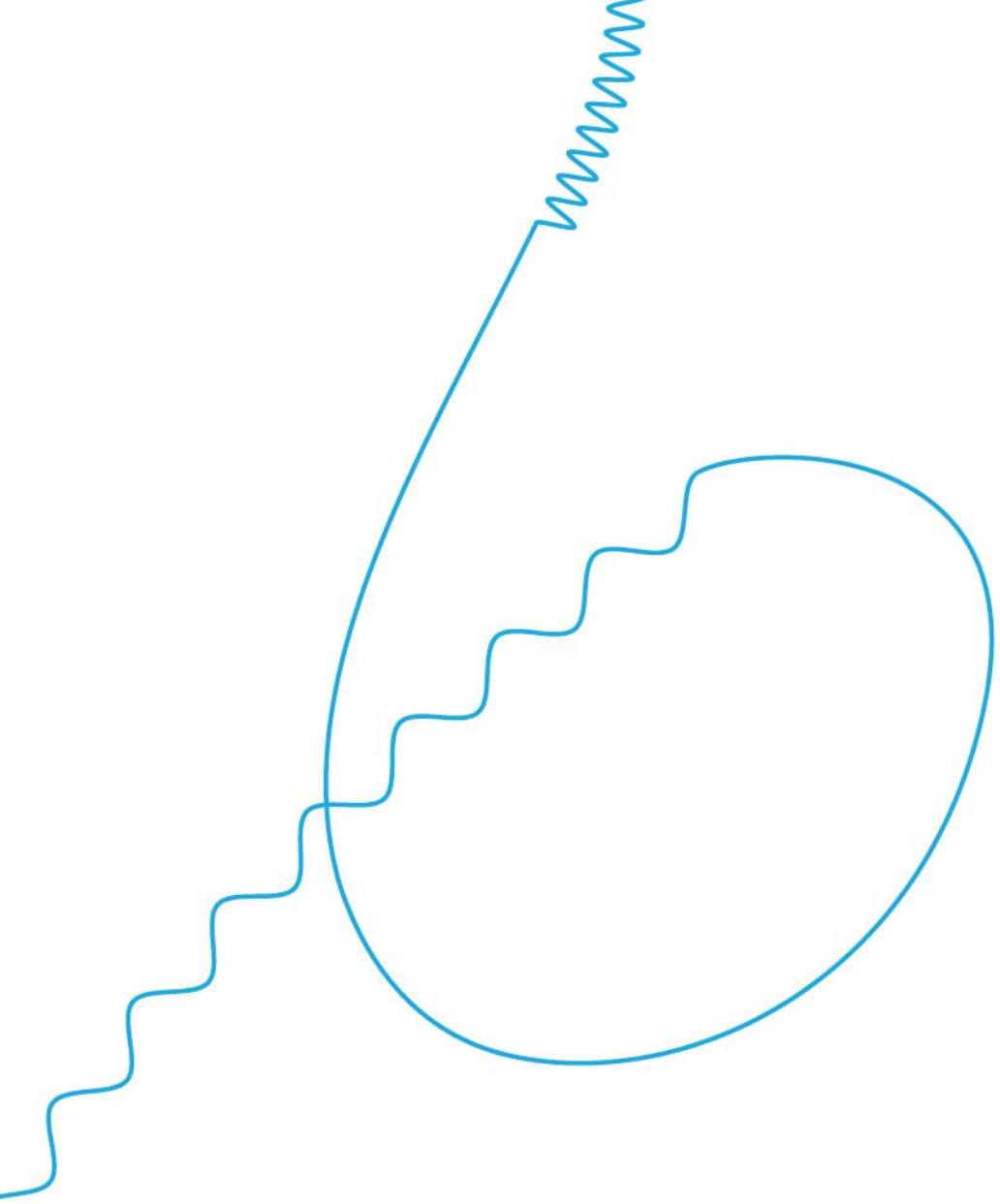


- Primary endpoint analysis **expected in 4Q 2022**

- Previous PD-1 studies show a **12-month RFS of 70-75%**
- Goal to show an **improved benefit in PCV + pembrolizumab arm** compared to pembrolizumab (SOC)

Today's agenda

Introduction	**Stéphane Bancel**, *Chief Executive Officer*
R&D Day 2022 Overview	**Stephen Hoge, M.D.**, *President*
mRNA Therapeutics	
Rare Diseases • Organic acidemias overview and real-world burden of disease • Interim PA Phase 1/2 data • Interim GSD1a Phase 1/2 data	**Dr. Mark S. Korson,** *Director of Physician Support Service and Education, VMP Genetics* **Ruchira Glaser, M.D.**, *SVP, Head, Therapeutics (Rare Disease, Autoimmune & Emerging)* **Geoffrey Rezvani, M.D.,** *Executive Director, Program Leader (Cardiovascular and Emerging Therapeutics)*
Immune Oncology • Personalized Cancer Vaccine (Phase 2 trial overview)	**Michelle Brown, M.D., Ph.D.,** *Executive Director, Program Leader, Oncology*
Coffee Break (10 minutes)	
Vaccines: Late-Stage Phase 3 Trials	
COVID Booster/Combination Respiratory Vaccines	**Jacqueline Miller, M.D.**, *SVP, Therapeutic Area Head, Infectious Diseases*
Seasonal Influenza Vaccine Phase 3 Trials	**Raffael Nachbagauer, M.D., Ph.D.,** *Senior Director, Infectious Disease Development*
Respiratory Syncytial Virus (RSV) Phase 3 Trial	**Christine Shaw, Ph.D.,** *VP, Portfolio Head Respiratory Vaccines, Infectious Disease Development*
Cytomegalovirus (CMV) Vaccine Phase 3 trial	**Jacqueline Miller, M.D.**, *SVP, Therapeutic Area Head, Infectious Diseases*
Commercial Organization Launch Preparation	**Arpa Garay,** *Chief Commercial Officer*
Conclusion	**Stéphane Bancel**, *Chief Executive Officer*
Q&A	**Stéphane Bancel, Stephen Hoge, Arpa Garay, Ruchira Glaser, Jacqueline Miller, Praveen Aanur**



COVID Boosters & Respiratory Combination Vaccines

Jacqueline Miller, M.D.

SVP, Therapeutic Area Head, Infectious Diseases

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Moderna has launched two vaccine boosters to meet different market needs across the largest markets

mRNA-1273.214

(25 µg of mRNA-1273 and 25 µg of Omicron BA.1)

- Induced significantly higher titers than mRNA-1273 against the BA.1 and BA.4/5 sublineages in a clinical trial conducted before the fall booster season
- Authorized in United Kingdom, Switzerland, Australia, Canada and European Union (conditional)

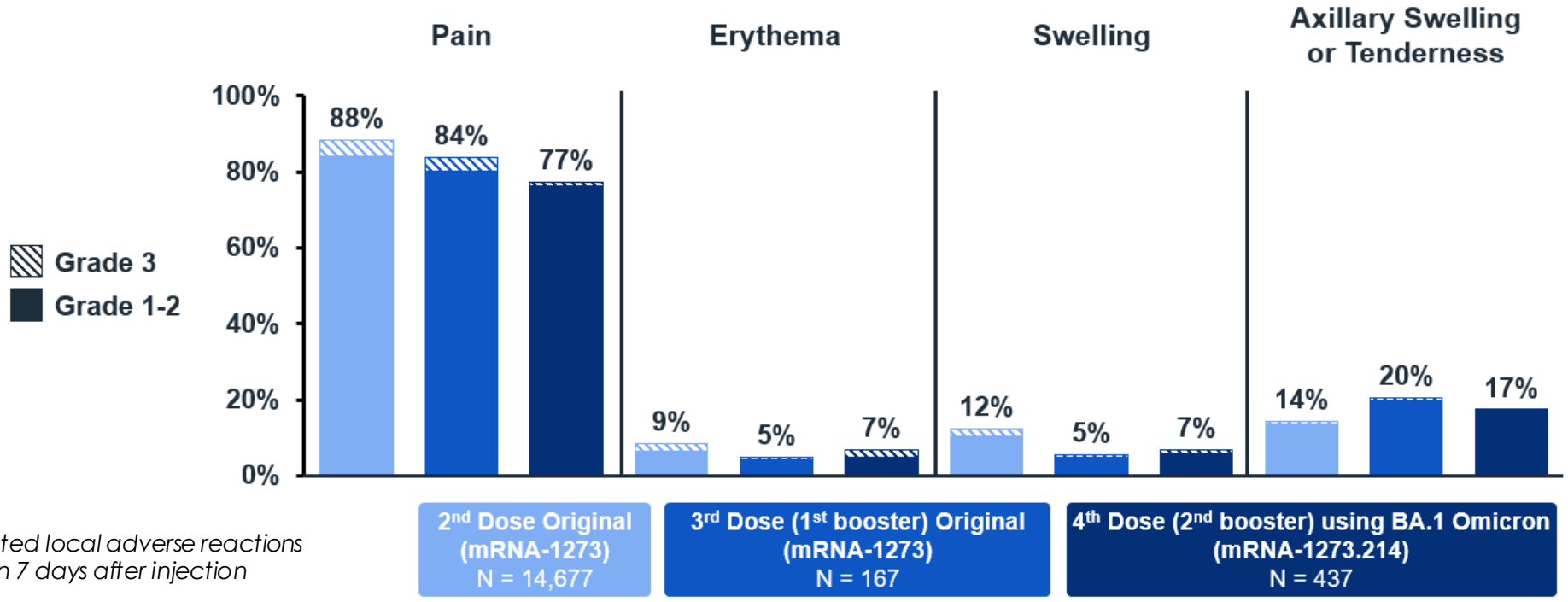
mRNA-1273.222

(25 µg of mRNA-1273 and 25 µg of Omicron BA.4/5)

- Based on the BA.4/5 strain and is being developed consistent with recent FDA guidance
- Authorized in United States

Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

Local reactogenicity of BA.1 Omicron bivalent (mRNA-1273.214) as 4th dose similar to 2nd dose of primary series and 3rd dose of original (mRNA-1273) in adults



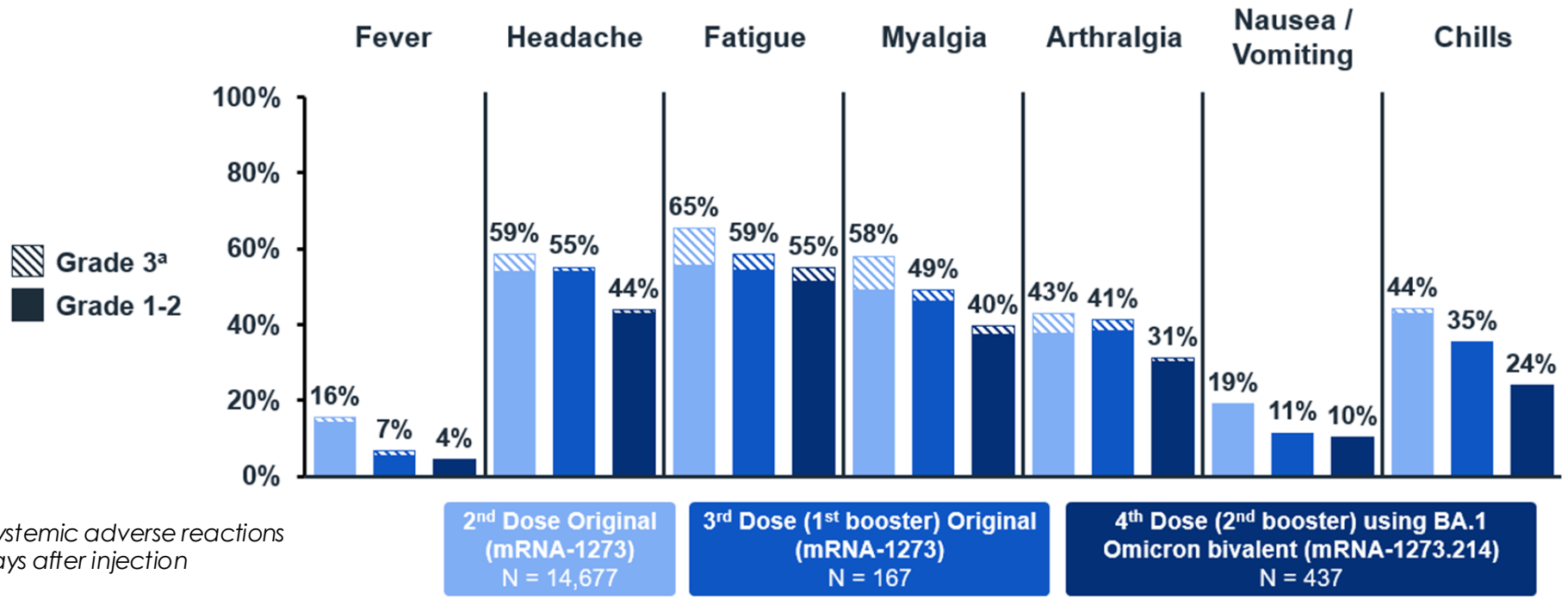
Solicited local adverse reactions within 7 days after injection

No Grade 4 events reported

2nd dose mRNA-1273 (Baden et al, NEJM 2021); 3rd dose mRNA-1273 (Choi et al, Nat Med 2022); 4th dose mRNA-1273.214 (Chalkias et al. medRxiv 2022; in press New Engl J Med)

Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

Systemic reactogenicity of BA.1 Omicron bivalent (mRNA-1273.214) as 4th dose generally lower than 2nd dose of primary series and 3rd dose of mRNA-1273 in adults



Solicited systemic adverse reactions within 7 days after injection

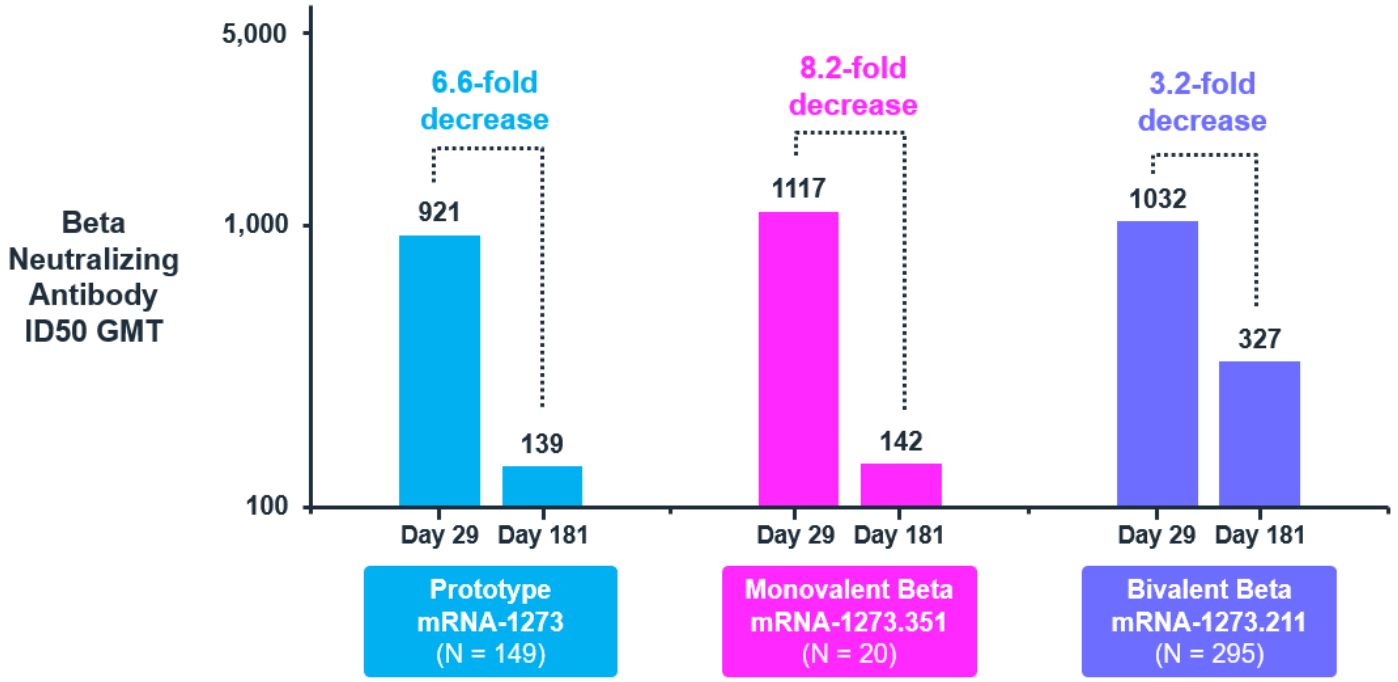
Grade 4 systemic reactions only with 2nd dose of mRNA-1273 (<0.1%)

2nd dose mRNA-1273 (Baden et al, NEJM 2021); 3rd dose mRNA-1273 (Choi et al, Nat Med 2022); 4th dose mRNA-1273.214 (Chalkias et al. medRxiv 2022; in press New Engl J Med)

Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

Bivalent Beta vaccine (mRNA-1273.211) as 3rd dose elicited higher neutralizing antibody responses in adults through 6 months compared to mRNA-1273 and monovalent Beta vaccine (mRNA-1273.351)

Neutralizing antibody responses against Beta in adults through 6 months



Chalkias et al. Research Square 2022, doi: 10.21203/rs.3.rs-1555201/v1.
Choi et al. Nature Med 2021;27:2025-2031.

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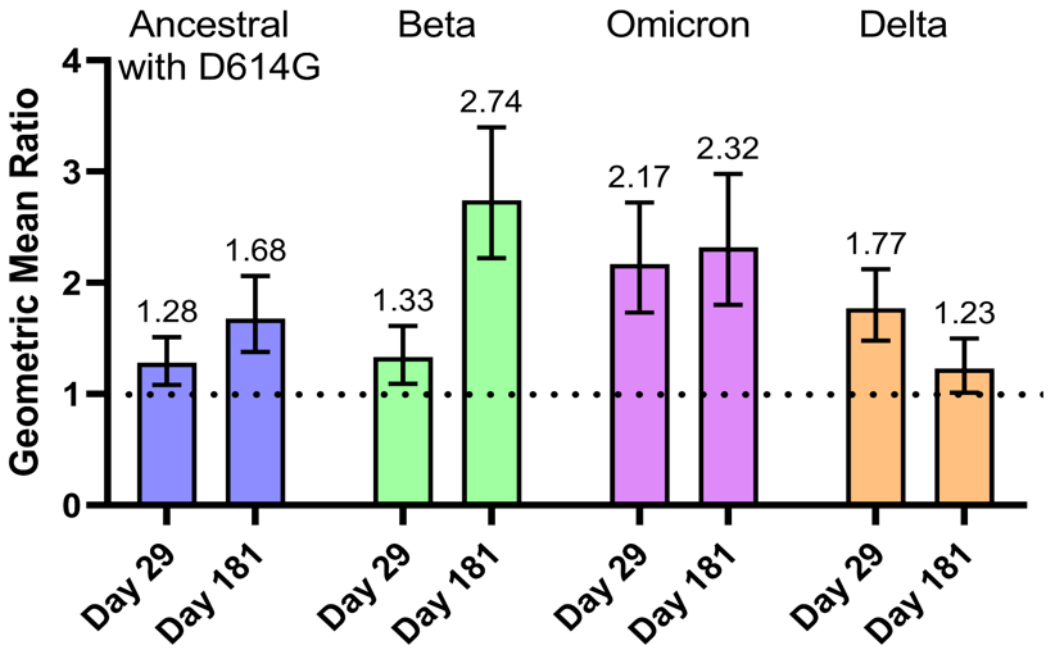
Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

Bivalent Beta vaccine (mRNA-1273.211) as 3rd dose elicited higher neutralizing antibody responses in adults through 6 months compared to mRNA-1273

Neutralizing antibody responses in adults through 6 months



Chalkias et al. Research Square 2022, doi: 10.21203/rs.3.rs-1555201/v1–in press Nature Medicine

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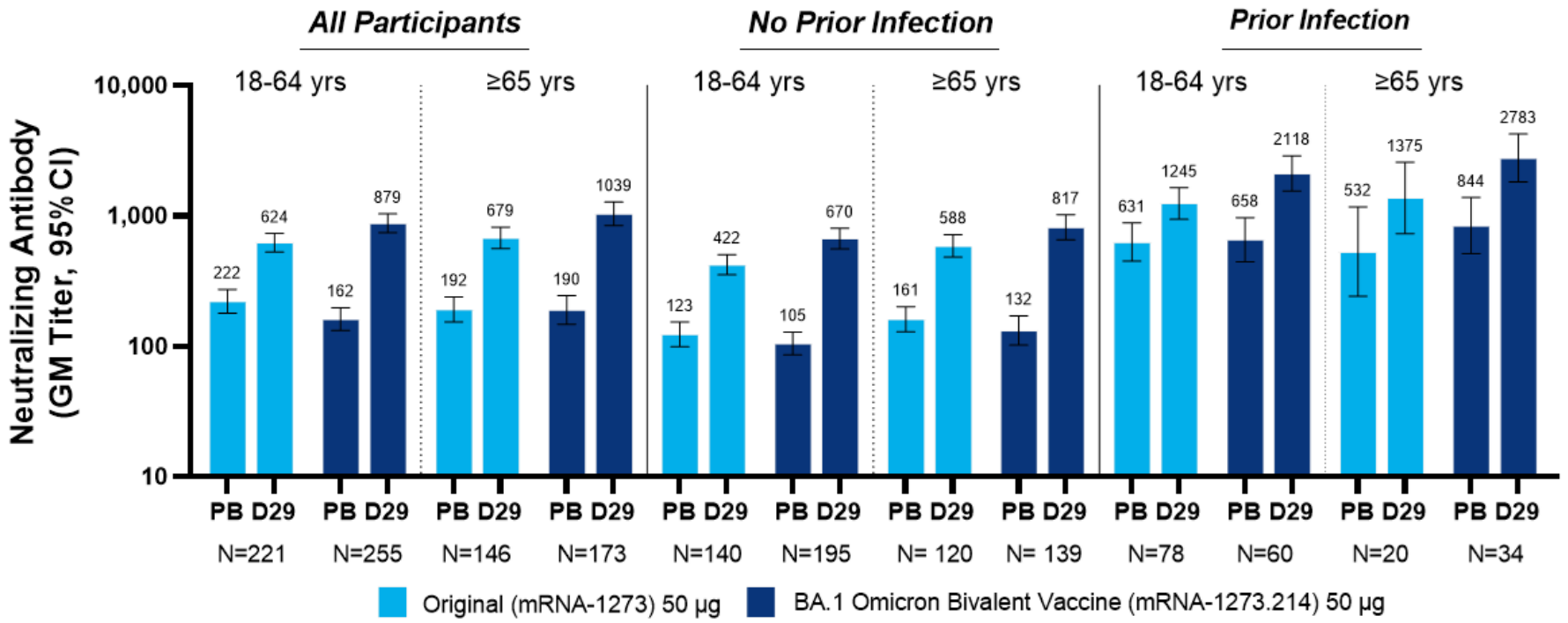
Clinical data from Beta/1273 and Omicron BA.1/1273 supports COVID bivalent platform and .222 submission

4th dose (2nd booster) with BA.1 Omicron bivalent booster (mRNA-1273.214) resulted in higher neutralizing antibody titers against Omicron BA.4/BA.5 across age groups, including ≥65-year-olds, than mRNA-1273

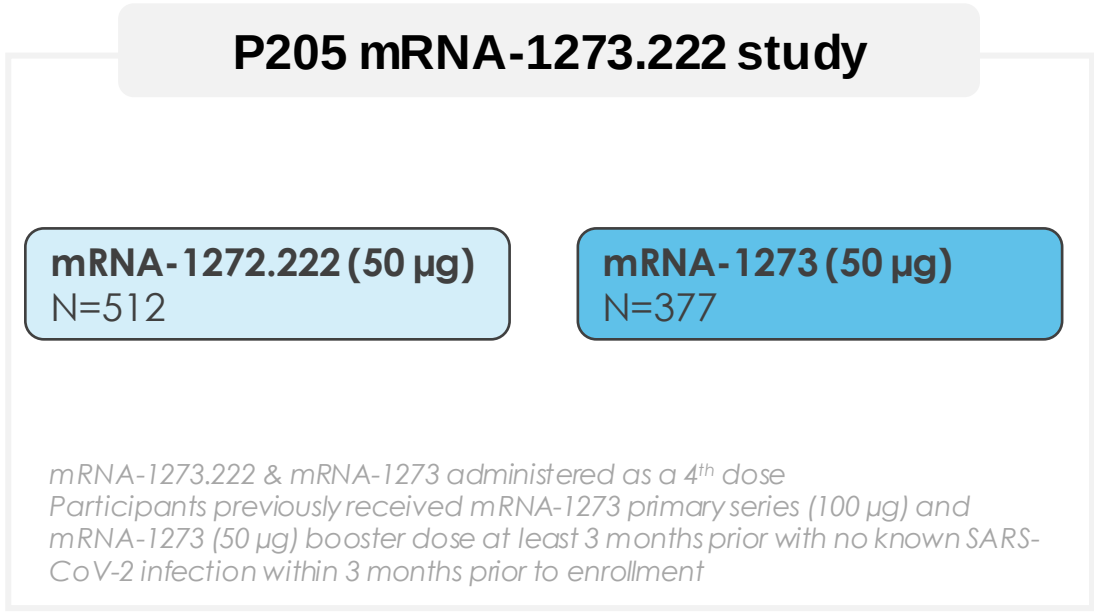
Neutralizing antibody responses in adults through 1 month



Pre-booster (PB), Day 29 post-boost (D29)

BA.4/5 Omicron-targeting bivalent booster (mRNA-1273.222) ongoing in a clinical study

- **mRNA-1273.222 arm fully enrolled** on August 25th
- **Primary objectives**
  - Safety, reactogenicity
  - Immunogenicity: neutralizing antibody response **comparison of .222 50 µg vs. mRNA-1273 50 µg (historical comparator) against BA.4/5** when administered as 4th doses based on GMR and SRR-difference



GMR: Geometric mean ratio
SRR: Seroconversion response ratio

Advantages of mRNA platform accelerates authorization of up-to-date boosters

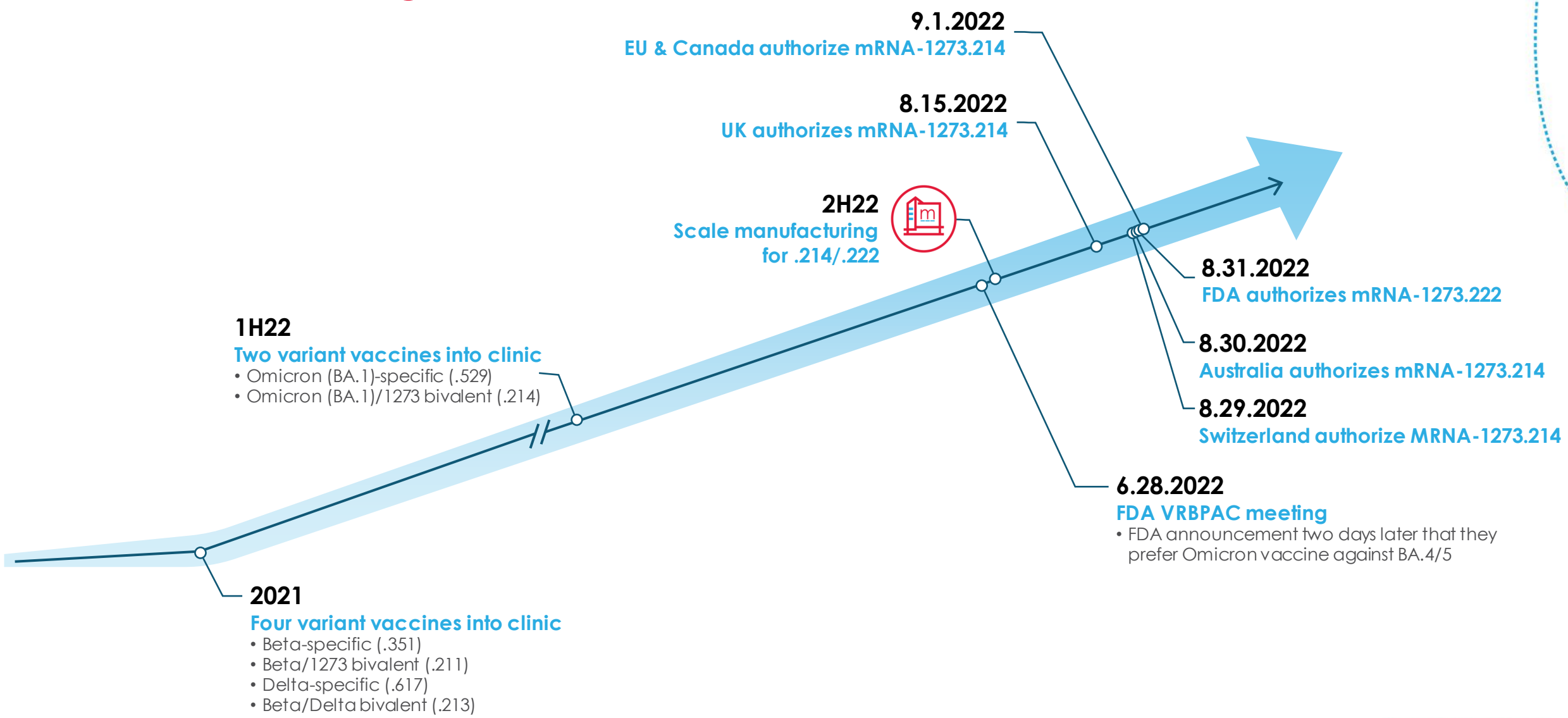
We can **simultaneously move COVID variant boosters into the clinic and prepare for launches** because we can leverage:

Clinical data generated from bivalent platform: Advanced multiple variant booster vaccines (Beta, Delta, Omicron and bivalents)

Chemistry, manufacture and control data: Manufacturing process and inputs are the same across vaccines

Preclinical data: Models in mice have translated effectively to clinical data

mRNA platform allows for rapid development and manufacturing timelines

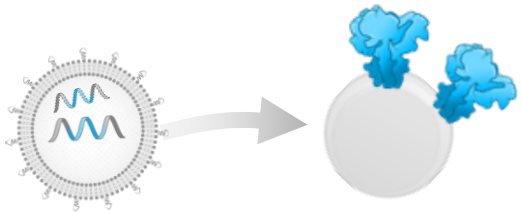


Rapid licensure of vaccines against COVID sets the stage for respiratory vaccines and combinations

mRNA-1273 licensed

COVID (mRNA-1273)

.214, .222

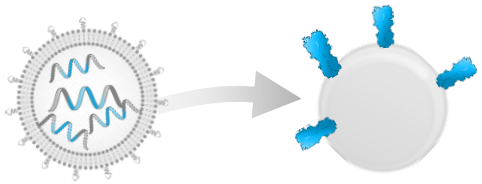


SARS-CoV-2 spike protein

Omicron (BA.1) variant + wild-type,
Omicron (BA.4/5) variant + wild-type

- Bivalent vaccine
- 50 µg booster dose level in adults
- Observed higher effectiveness in real-world evidence (RWE)

Seasonal Flu (mRNA-1010)

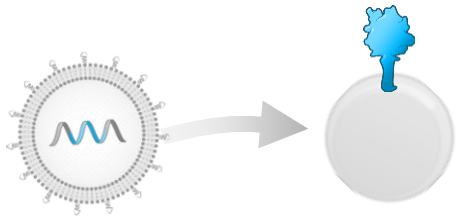


HA glycoproteins

(A/H1N1, A/H3N2 and influenza B/Yamagata and B/Victoria lineages)

- Quadrivalent vaccine
- 50 µg dose level in adults
- 18+ immunogenicity Ph 3 study ongoing
- 50+ efficacy Ph 3 study planned for fall 2022

RSV (mRNA-1345)



RSV Prefusion F protein

- Monovalent vaccine
- 50 µg dose level in adults
- 60+ efficacy Ph 2/3 study ongoing
- 50+ immunogenicity Ph 3 study ongoing

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Combination vaccines in pipeline to leverage efficacy of standalone vaccines

Current combination pipeline

Older adults

- COVID + flu (mRNA-1073) fully enrolled in Phase 1/2
- COVID + flu + RSV (mRNA-1230) in preclinical

Pediatrics

- hMPV + PIV3 (mRNA-1653) in Phase 1
- RSV + hMPV (mRNA-1365) in preclinical

Running co-administration studies to help prepare for launches

Phase 3 randomized, observer-blind study

NIH U.S. National Library of Medicine
ClinicalTrials.gov
NCT05330975

Evaluating **safety, tolerability and immunogenicity of mRNA-1345**, an mRNA vaccine targeting respiratory syncytial virus (RSV), when **given alone or co-administered with a seasonal influenza vaccine or SARS-CoV-2 vaccine** in adults ≥ 50 years of age

Co-administration arms

RSV vaccine (mRNA-1345)	+	Seasonal influenza vaccine (Afluria® quadrivalent)
RSV vaccine (mRNA-1345)	+	COVID booster (mRNA-1237.214)

https://clinicaltrials.gov/ct2/show/NCT05330975?term=mRNA-1345&draw=2&rank=3

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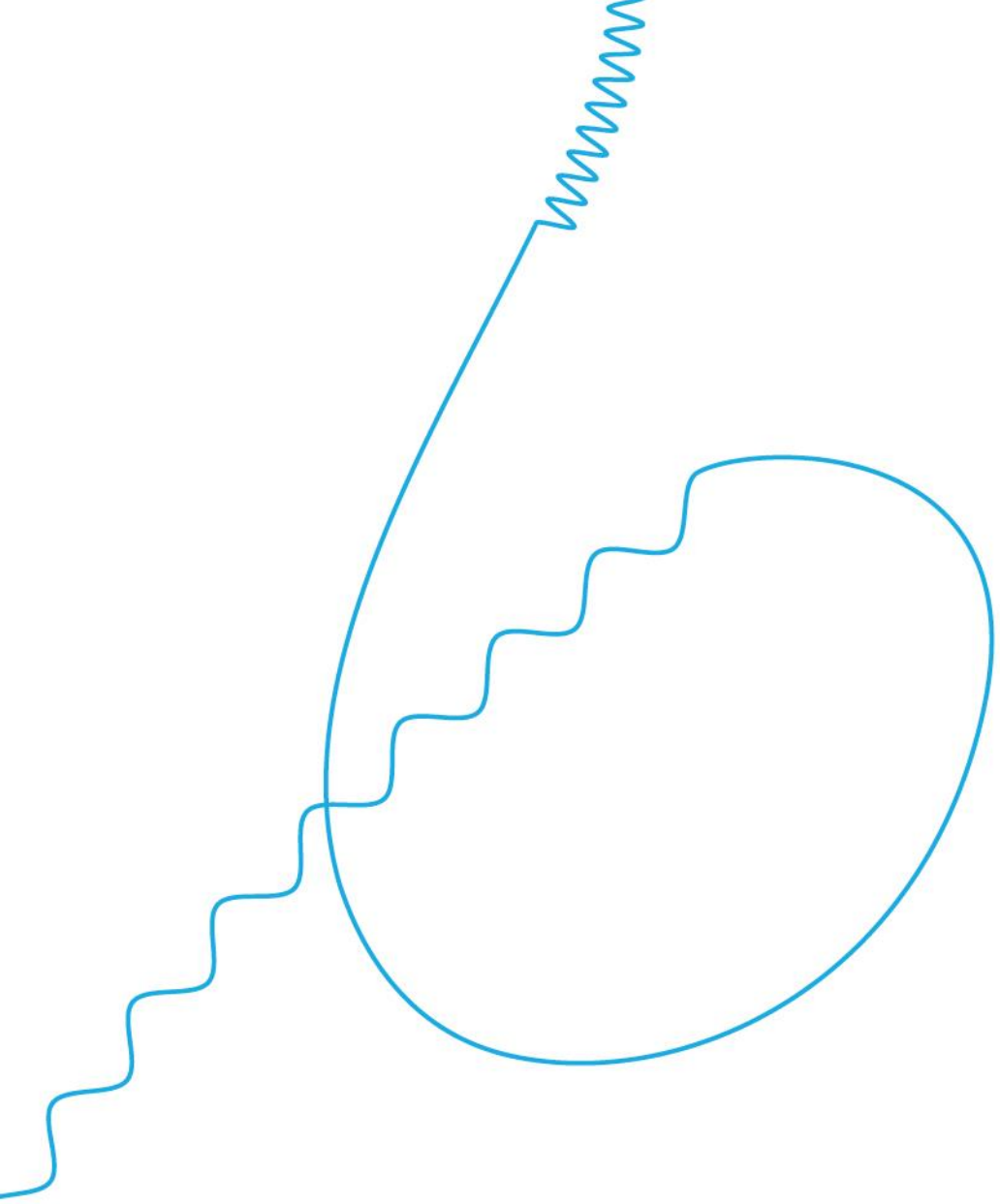

Seasonal Flu Vaccine Program

Raffael Nachbagauer, M.D., Ph.D.

Senior Director, Infectious Disease Development

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Seasonal influenza (flu) overview

Influenza (influenza A and influenza B) occurs seasonally and varies in severity each year, causing respiratory illnesses and placing a substantial burden on healthcare systems

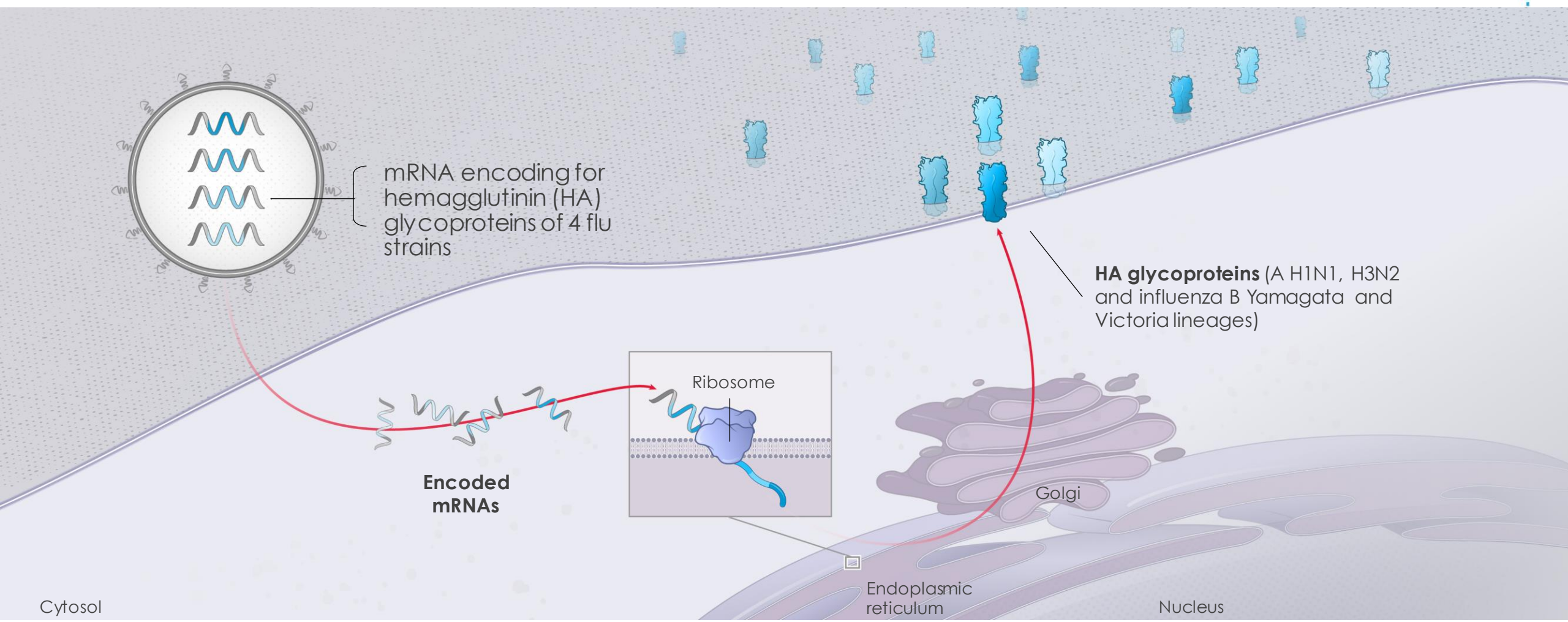
Disease burden:

- Worldwide, there are 3-5M severe cases of influenza and 290-650K influenza-related respiratory deaths annually[1]
- About 8% of the US population experiences symptoms from influenza each year, with 140-710K hospitalizations and 12-52K deaths per year[2]
- Peak influenza activity is seen in temperate climates during fall to winter and is reflected in increased outpatient visits, urgent care visits, and hospitalizations

Influenza symptoms & complications	
Symptoms	Fever Cough Sore throat Nasal congestion Fatigue Vomiting/diarrhea (more common in children)
Complications	Pneumonia (viral and/or bacterial) Ear infections Sinus infections Exacerbation of chronic conditions (e.g. asthma, heart failure)

1. World Health Organization. Influenza (Seasonal). WHO. 2018. https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)
2. Centers for Disease Control and Prevention. Disease burden of influenza. Available at: https://www.cdc.gov/flu/about/burden/index.html

mRNA-1010 is our influenza vaccine candidate furthest advanced in clinical development



1:1:1:1 ratio for mRNA sequences encoding HAs of 4 strains (A/H1N1, A/H3N2, B/Victoria and B/Yamagata)

Two Phase 3 studies will support licensure of mRNA-1010

Immunogenicity trial in Southern Hemisphere ongoing; efficacy trial in Northern Hemisphere expected to start in the fall

Immunogenicity trial

- Study ongoing in Southern Hemisphere
- Targeted enrollment of 6,000 participants
  - Fully enrolled study in August
- Study intended to support initial licensure based on demonstrated safety and immunogenicity; received favorable feedback from FDA and EMA

Efficacy trial

- Will be conducted in Northern Hemisphere
- Study start planned for this fall
- Expected to enroll approximately 23,000 participants
- Intended to fulfill post-licensure requirement to demonstrate efficacy after initial approval based on immunogenicity

mRNA-1010 Phase 3 immunogenicity study in adults 18+ is fully enrolled

IGNITE
Influenza mRNA Vaccine Study

- **Number of participants: ~6,000**
  - ~30% of participants ≥ 50 to < 65 years old
  - ~20% of participants ≥ 65 years old
- **Primary endpoints**
  - Safety
  - Non-inferior immunogenicity (GMT and seroconversion rate)
- **Secondary endpoints**
  - Superior immunogenicity
- **Site locations**
  - Australia, Argentina, Colombia, Panama and Philippines

Ph 3 immunogenicity study design

mRNA-1010 (50 µg)
N=3,000

Active comparator
N=3,000

2022 Southern Hemisphere vaccine composition

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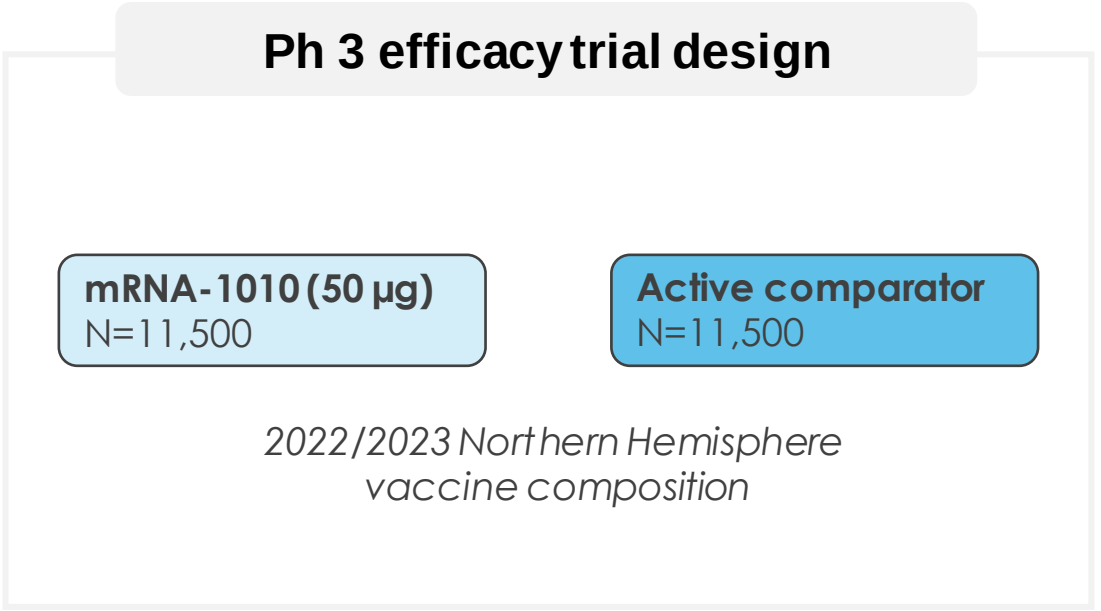
mRNA-1010 Phase 3 efficacy study in adults 50+

Expected to start in fall 2022

- **Number of participants: 23,000**
  - Approximately 50% will be 65+ and ~10% will be 75+
- **Primary endpoints**
  - Non-inferior (NI) relative vaccine efficacy (rVE) in preventing first episode of RT-PCR-confirmed protocol-defined influenza-like illness (ILI) caused by any strain of influenza A or B
  - Safety
- **Secondary endpoints**
  - Superior rVE in preventing first episode of RT-PCR-confirmed protocol-defined ILI caused by any strain of influenza A or B
  - rVE based on additional definitions
  - rVE to prevent hospitalization associated with influenza illness
- **Study duration**
  - Approximately one year of follow up
  - Efficacy studies can span multiple years

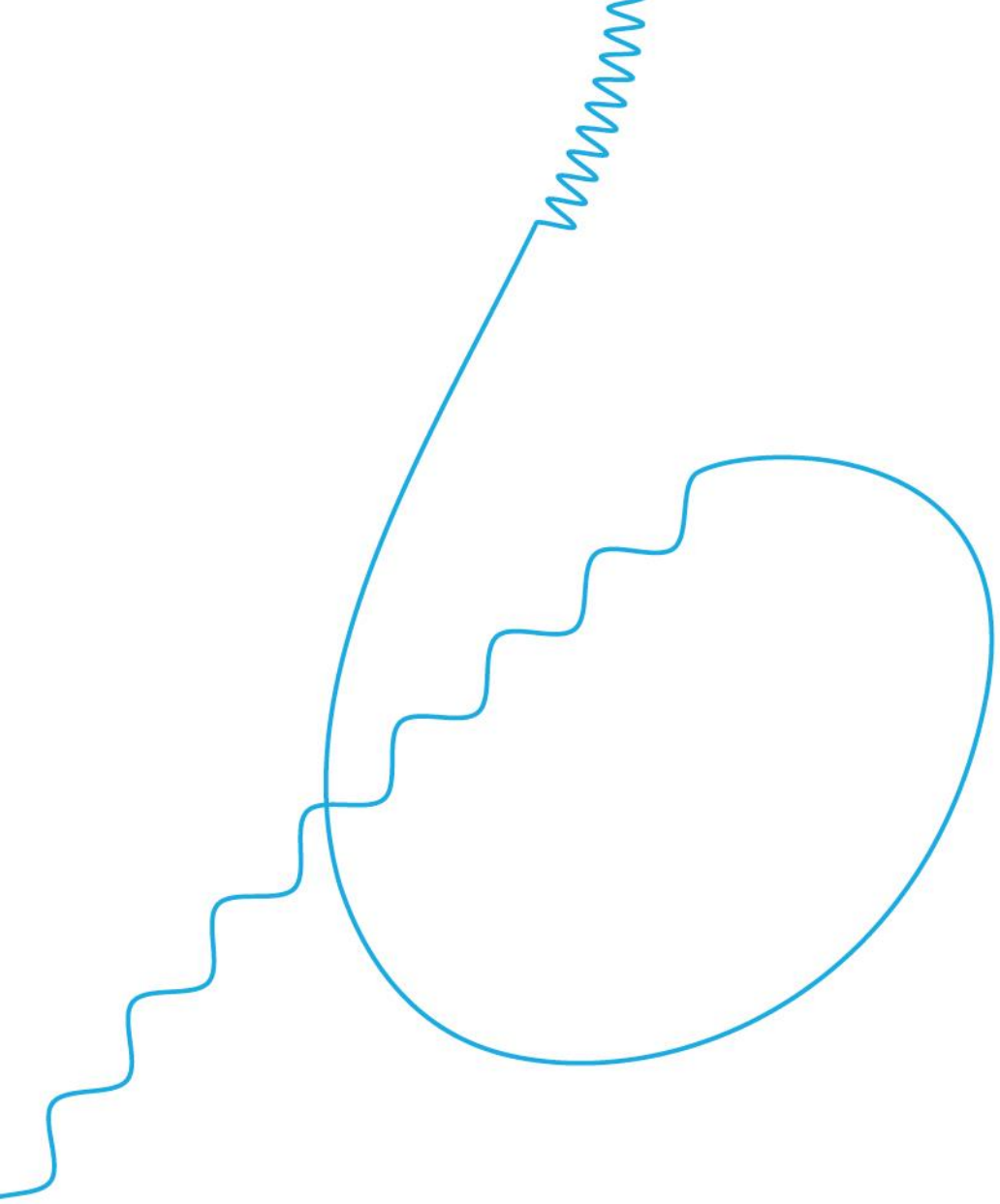


Flu vaccine program accelerating towards pivotal results

Phase 3 immunogenicity trial expected to read out in 1H23
Trial is expected to support initial licensure

Phase 3 efficacy trial in Northern Hemisphere expected to start fall 2022
Will fulfill regulatory requirement to demonstrate efficacy post-licensure

mRNA-1010 is our influenza candidate vaccine furthest in development
Additional candidates that encode for additional antigens (NA) already in the clinic (mRNA-1020/-30); candidates encoding for additional HAs for enhanced breadth planned for 2023 (mRNA-1011/-12)



Older Adults RSV Vaccine Program

Christine Shaw, Ph.D.

VP, Portfolio Head, Respiratory Vaccines, Infectious Disease Development

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Respiratory syncytial virus (RSV) is a large burden in older adults

RSV is a common seasonal respiratory virus

- There are **~177,000 hospitalizations** in adults 65+ due to RSV in the U.S. each year, and **~14,000 deaths**[1]
- Globally it is estimated that there are more than **1.5 million episodes of acute respiratory tract infection** and **~336,000 hospitalizations** related to RSV each year[2]
- RSV burden in older adults is **underestimated due to a lack of routine testing**[3]
- Annual cost of RSV hospitalizations in US adults aged ≥50 years is **estimated to be >$1 billion USD**[4]

Long-term RSV infection sequelae

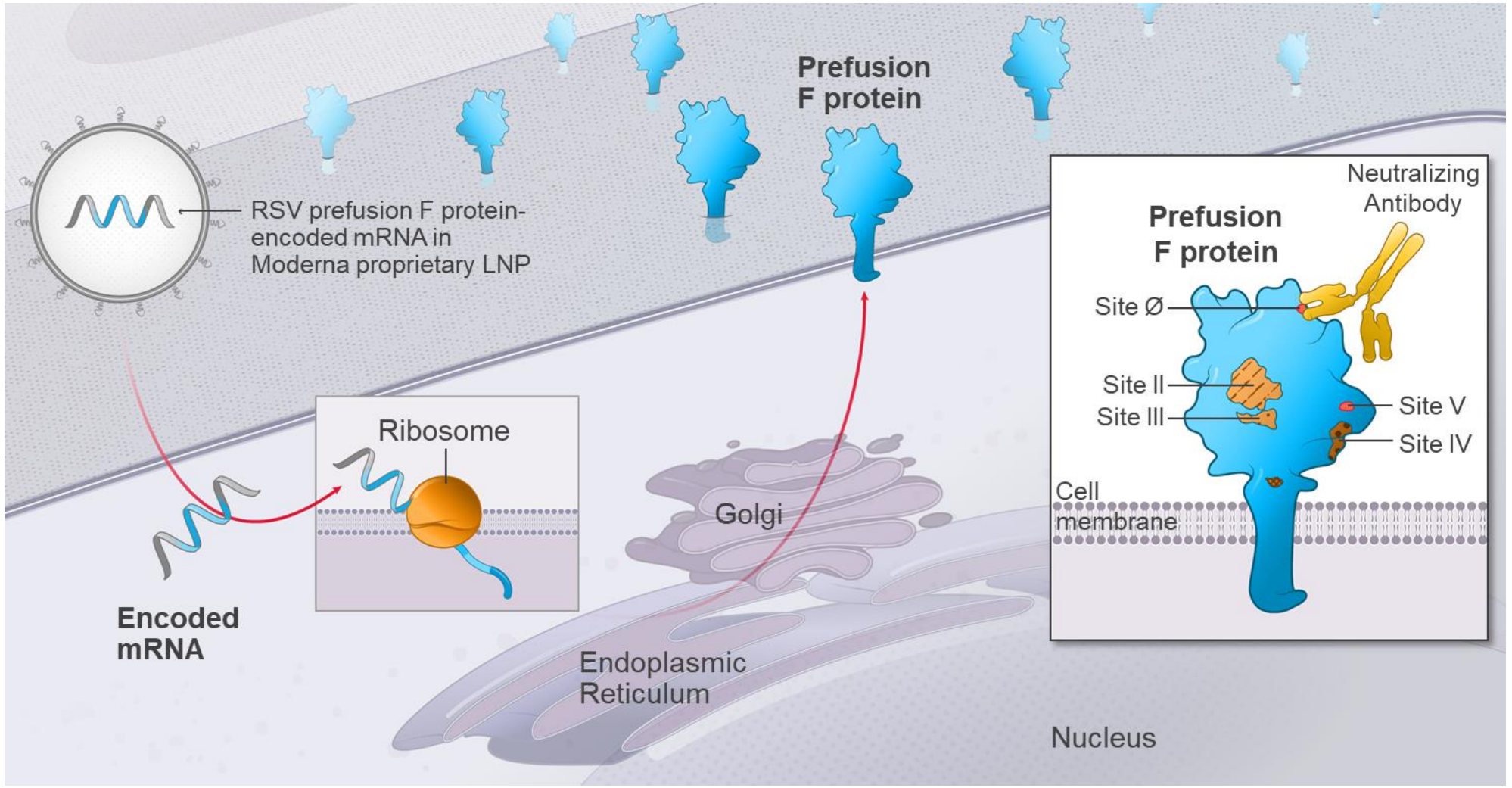
Severe acute respiratory infection and lower respiratory tract infections

Exacerbation of chronic obstructive pulmonary disease

Higher 1 year mortality after severe illness

1. RSV in Older Adults and Adults with Chronic Medical Conditions, CDC, https://www.cdc.gov/rsv/high-risk/older-adults.html
2. Shi, Ting, et al., *J Infect Dis.* (2020), https://doi.org/10.1093/infdis/jiz059
3. Li Y, et al. Lancet Infect Dis. 2021;21:1303-1312. 2. Griffiths C, et al. Clin Microbiol Rev. 2017;30(1):277-319
4. Choi Y, et al. Influenza Other Respir Viruses. 2022;16(1):151-158.

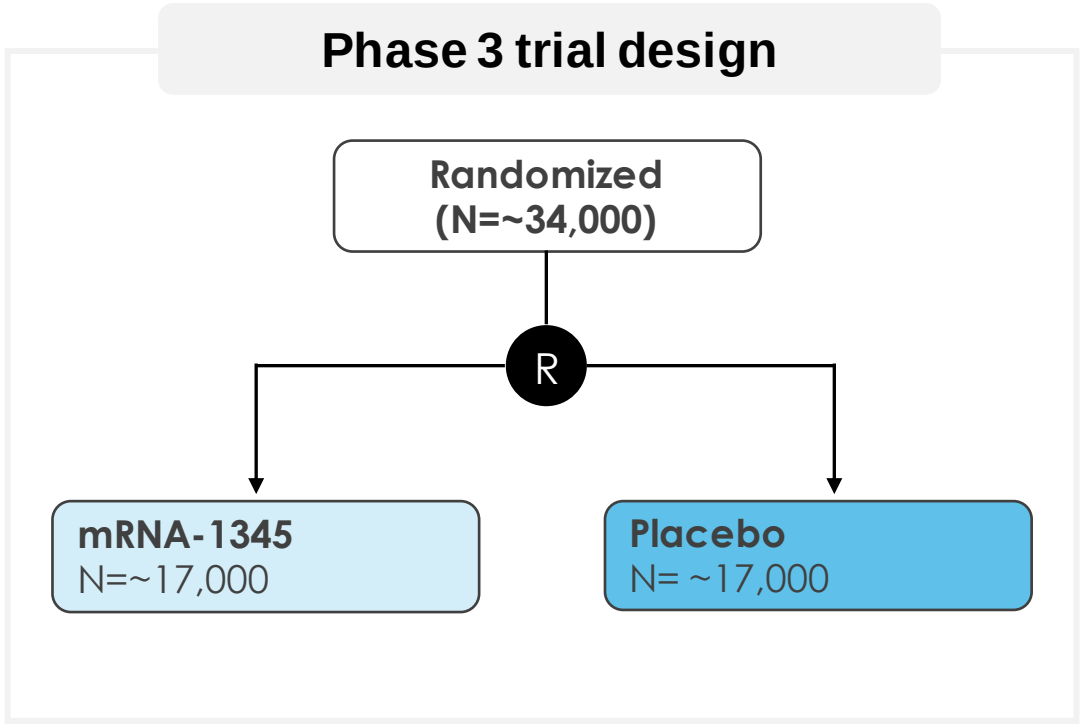
RSV vaccine (mRNA-1345) encodes a stabilized prefusion F glycoprotein



Pivotal Phase 3 trial in older adults has enrolled more than 24,000 participants

ConquerRSV

- **Pivotal Phase 3 efficacy study**
  - Adults ≥ 60 years of age
  - Placebo-controlled, case-driven design
- **Expect to enroll ~34,000 participants in multiple countries;** locations influenced by RSV epidemiology
  - Phase 2 portion enrolled ~2,000 participants
  - **Phase 3 portion started in February 2022** after DSMB review of Phase 2 portion
- Primary endpoints are **safety and vaccine efficacy**
- Primary efficacy analysis will be **triggered based on accrual of RSV cases**



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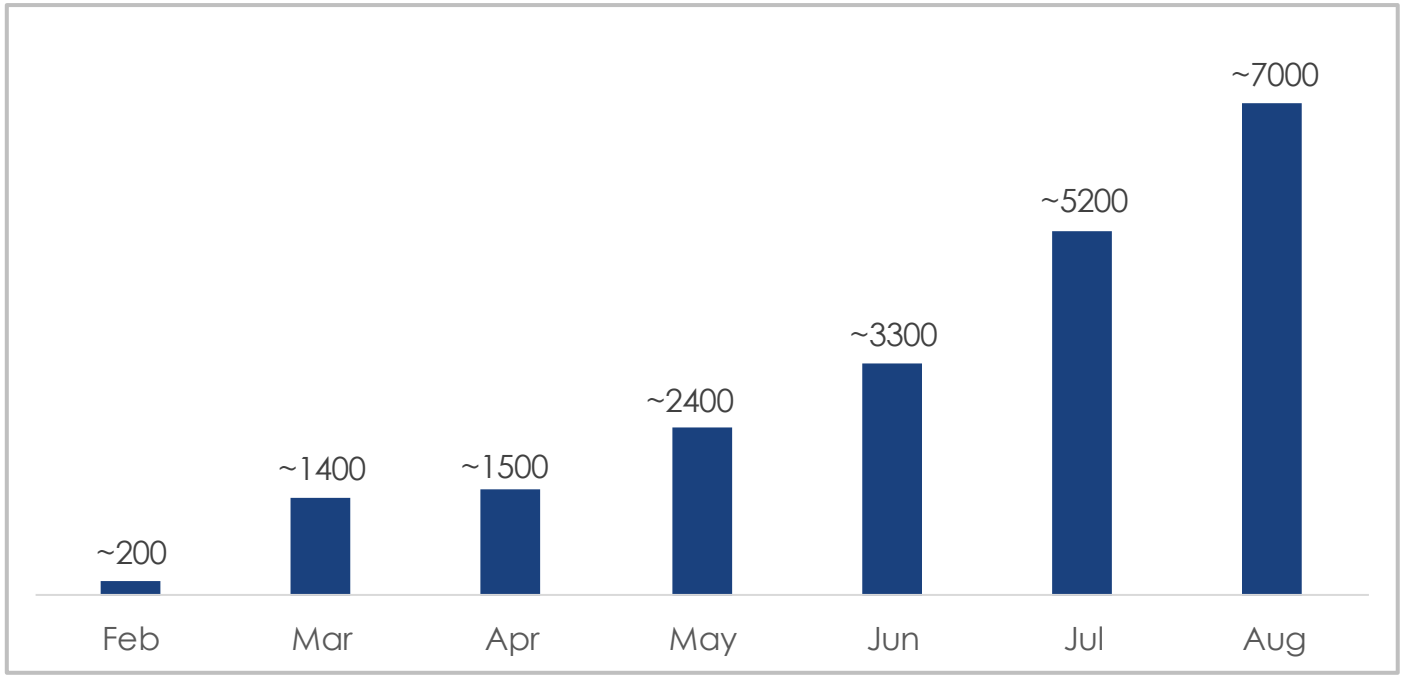
Enrollment is accelerating going into northern hemisphere fall/winter

Currently enrolled >24,000 subjects and enrollment is expected to complete this year

ConquerRSV

- Enrolling in 20 different countries
- Using global surveillance networks to follow RSV seasonality, which has been disrupted by the pandemic
- Sites set up in northern hemisphere ahead of expected fall/winter surge

Phase 3: Approximate enrollment per month



Total enrolled includes Phase 2 subjects that count to Phase 3 endpoint

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ConquerRSV trial is on track to meet D&I targets

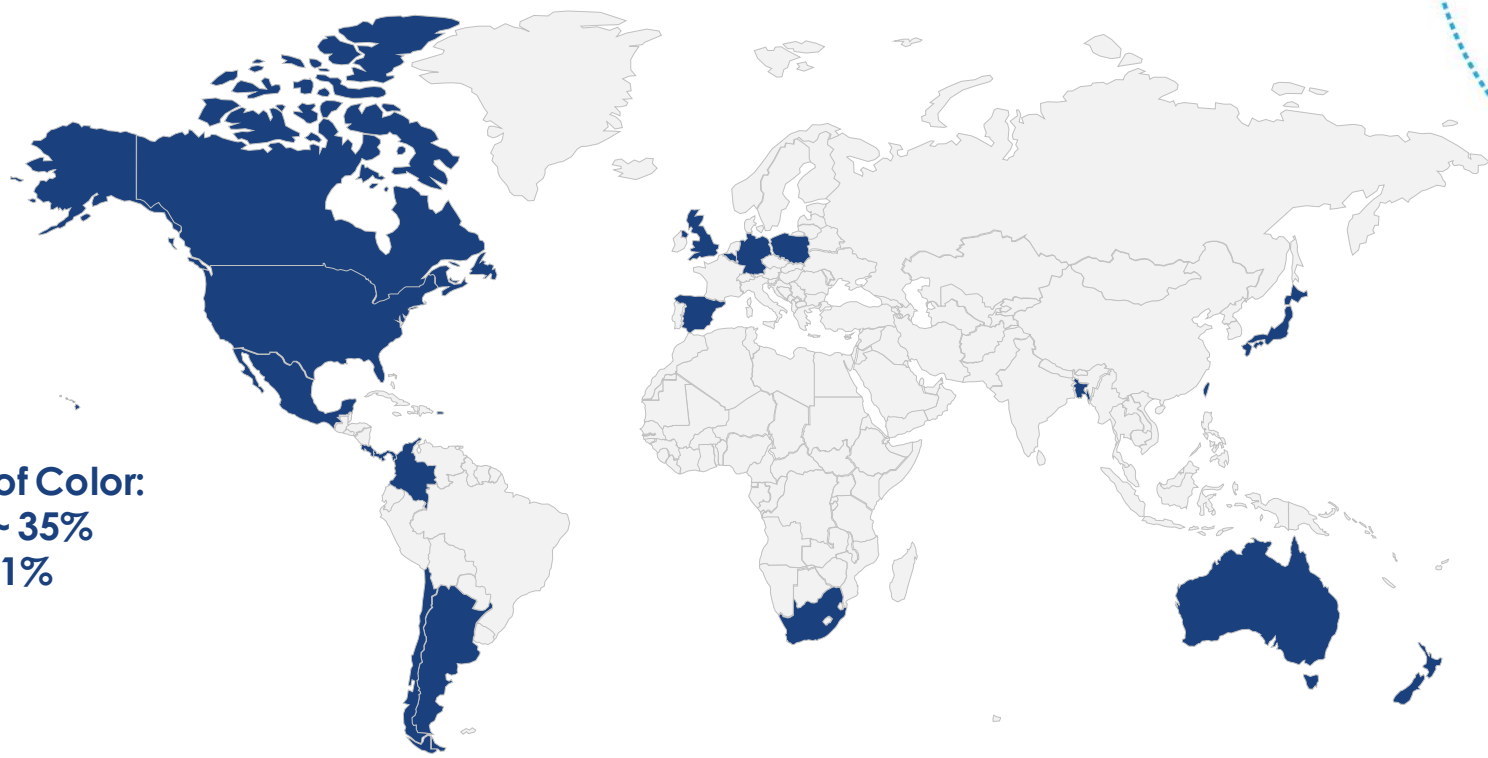
Currently enrolling in >200 sites in 20 countries

ConquerRSV

US Enrollment Based on Demographic Composition

	Current%
White, non-Hispanic	~ 65%
Hispanic/LatinX	~ 14%
Black or African American	~18%
Asian	~ 2%
Others	~ 1%

Persons of Color:
Current ~ 35%
Target 31%



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We will be evaluating endpoints across the spectrum of RSV clinical disease

ConquerRSV

- Throughout the trial, we will be **measuring multiple endpoints across the spectrum of RSV clinical disease**, including:
  - RSV lower respiratory tract disease (LRTD) with 2 or more signs/symptoms
  - RSV LRTD with 3 or more signs/symptoms
  - RSV-associated hospitalizations
  - RSV acute respiratory disease (ARD)
- Case accrual begins 14 days after vaccination
- Study is **designed and powered to accrue sufficient cases in one season** (fall/winter 2022-2023)
- In November, **we will have enough safety data to submit applications** (6 months safety for ~6,000 participants)

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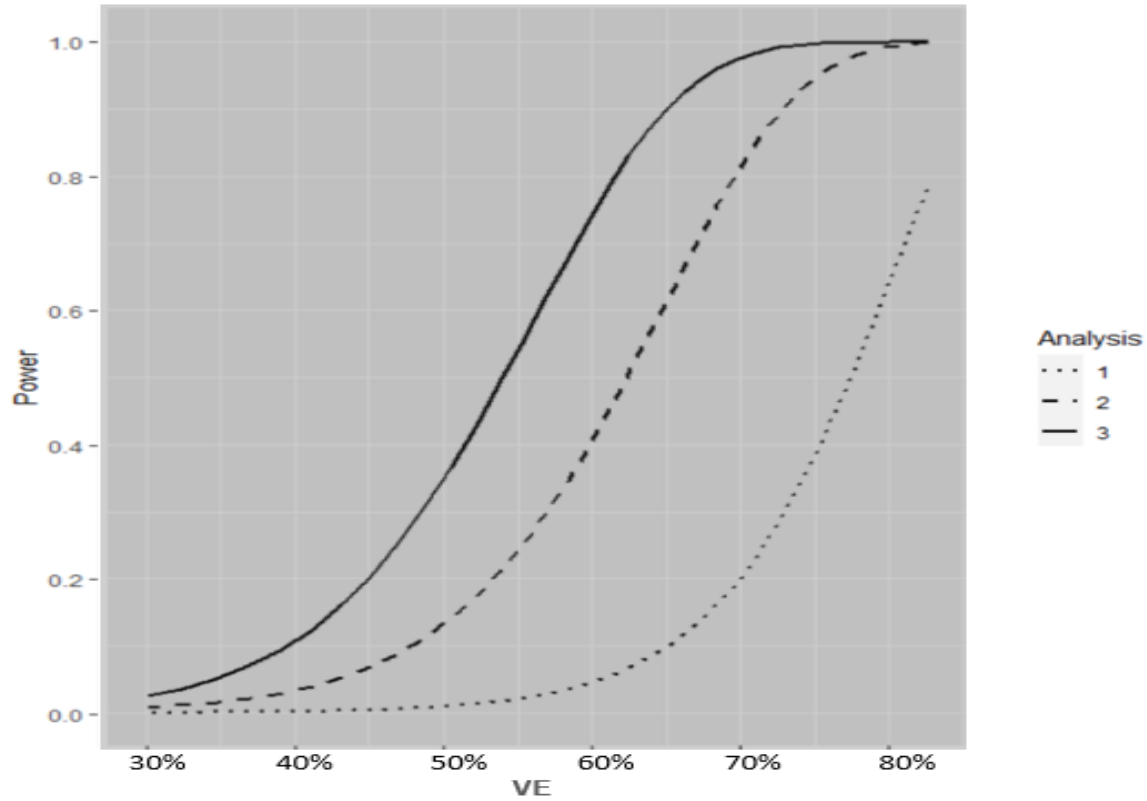
Overview of primary efficacy endpoint

Expect to reach enough cases for the first interim analysis this winter season (already accruing RSV cases in study)

ConquerRSV

Interim Boundaries Using O'Brien-Fleming Spending Function

	Approximate # of cases* (% of total cases)	VE: Efficacy bound
Interim analysis #1	43 (40%)	~0.76
Interim analysis #2	75 (70%)	~0.61
Primary analysis	106 (100%)	~0.53



** RSV LRTD with 2+ signs/symptoms*

LRTD: Lower-respiratory tract disease

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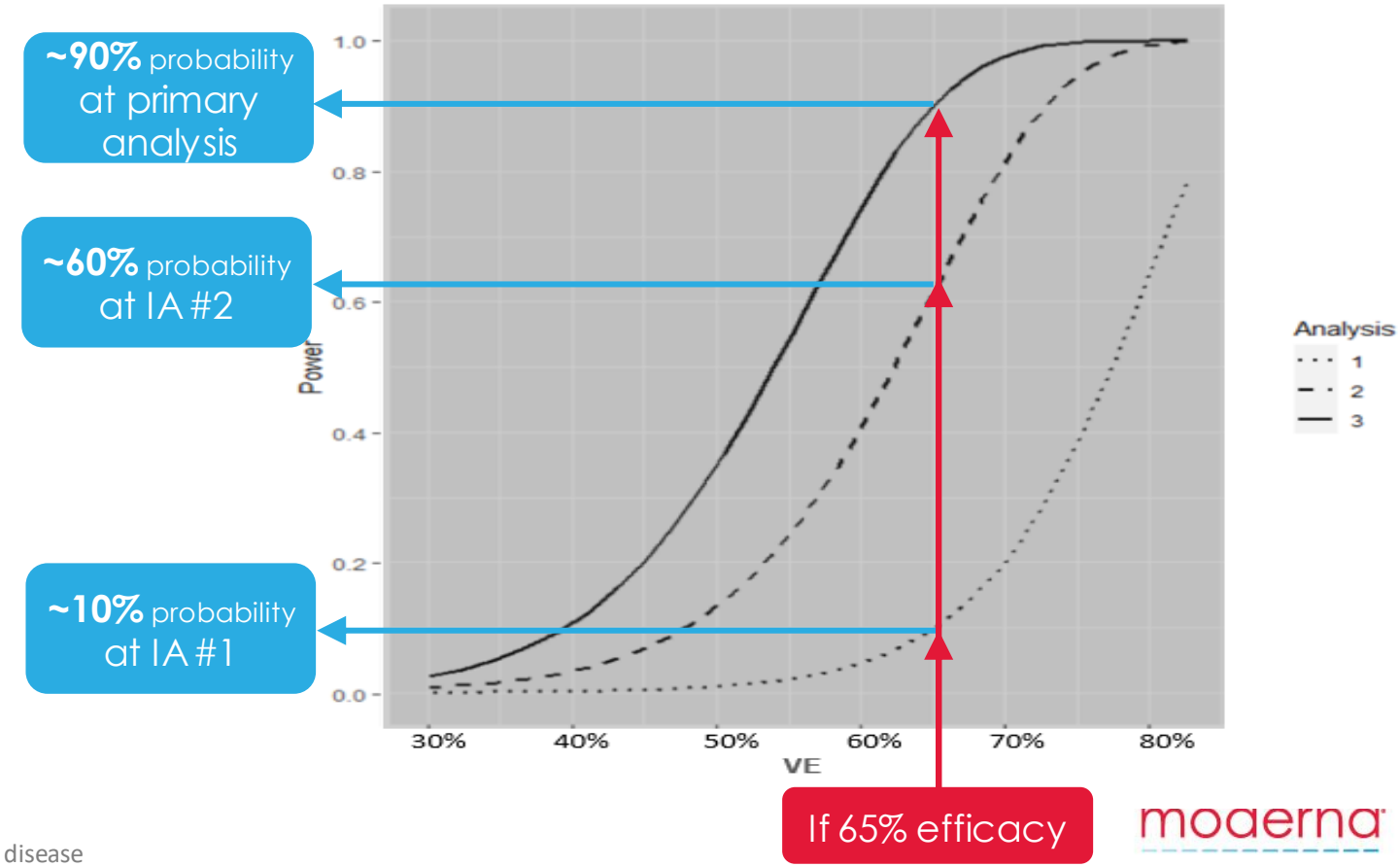

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LRTD: Lower-respiratory tract disease

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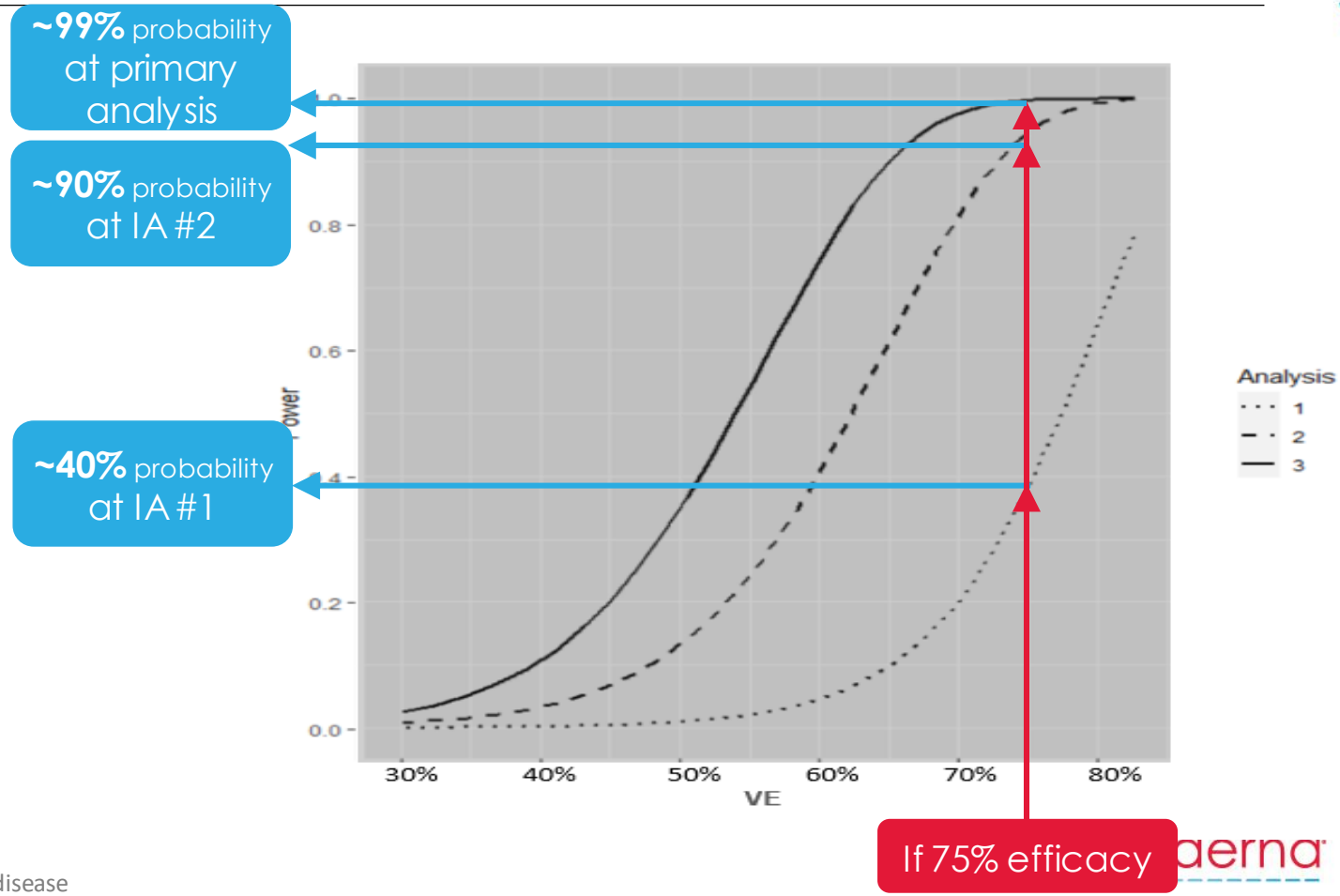


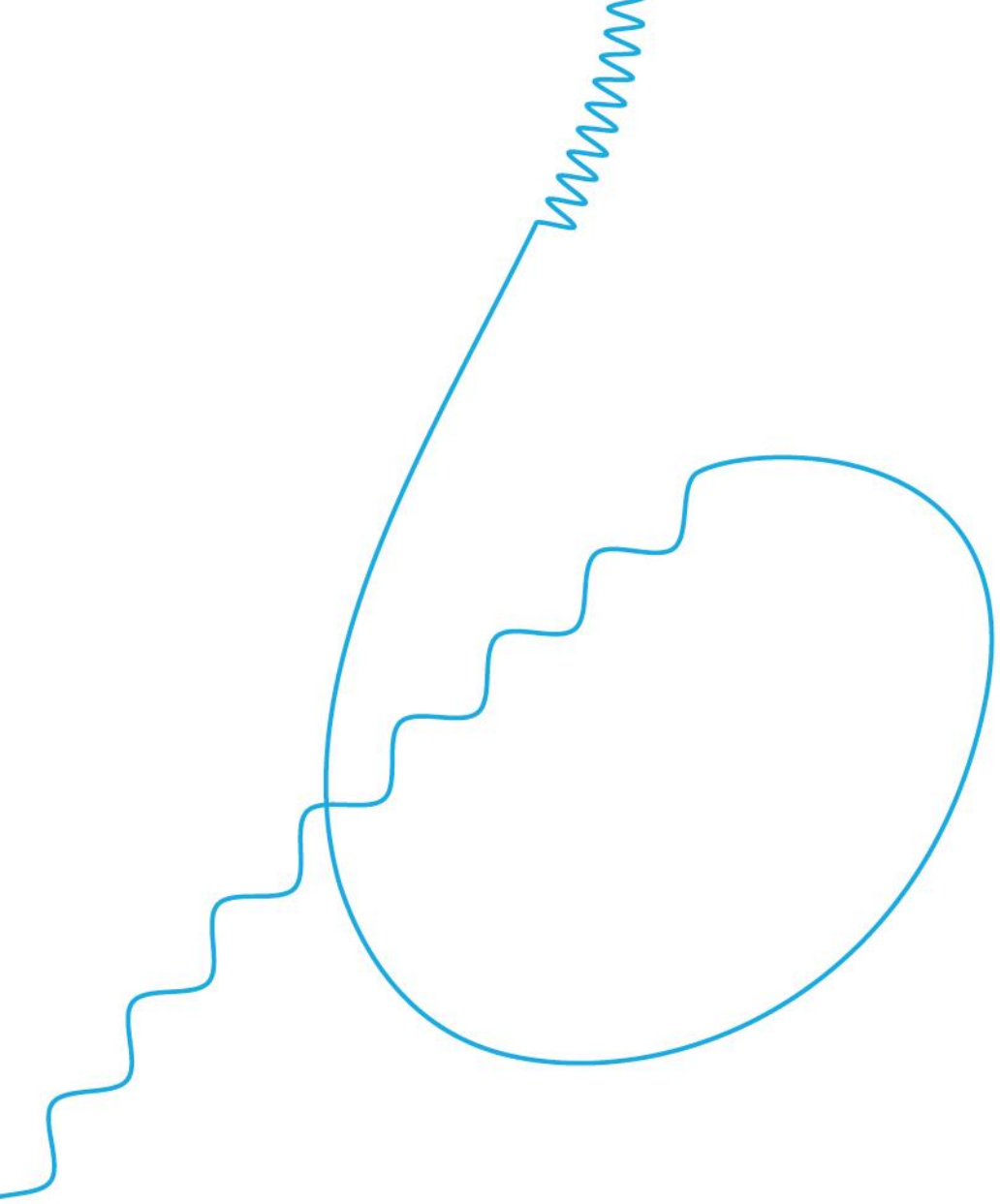
LRTD: Lower-respiratory tract disease

RSV vaccine (mRNA-1345) summary and next steps

Continuing to enroll more patients and open additional sites; ready for expected northern hemisphere RSV surge

Phase 3 efficacy trial could readout this winter, depending on number of cases accrued in the study and vaccine effectiveness; target safety follow up will be reached by November

mRNA-1345 is also ongoing in a Phase 1 trial in pediatric populations; RSV is also a large burden in the pediatric population



CMV Vaccine Program

Jacqueline Miller, M.D.

SVP, Therapeutic Area Head, Infectious Diseases

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Cytomegalovirus (CMV) Overview

Most common infectious cause of congenital sensorineural hearing loss worldwide

>$1B in annual healthcare costs[1]

Sequelae include:

- At birth: microcephaly, chorioretinitis, seizures, sensorineural hearing loss
- Long term: cognitive impairment, cerebral palsy, seizure disorder, sensorineural hearing loss

1 in 200

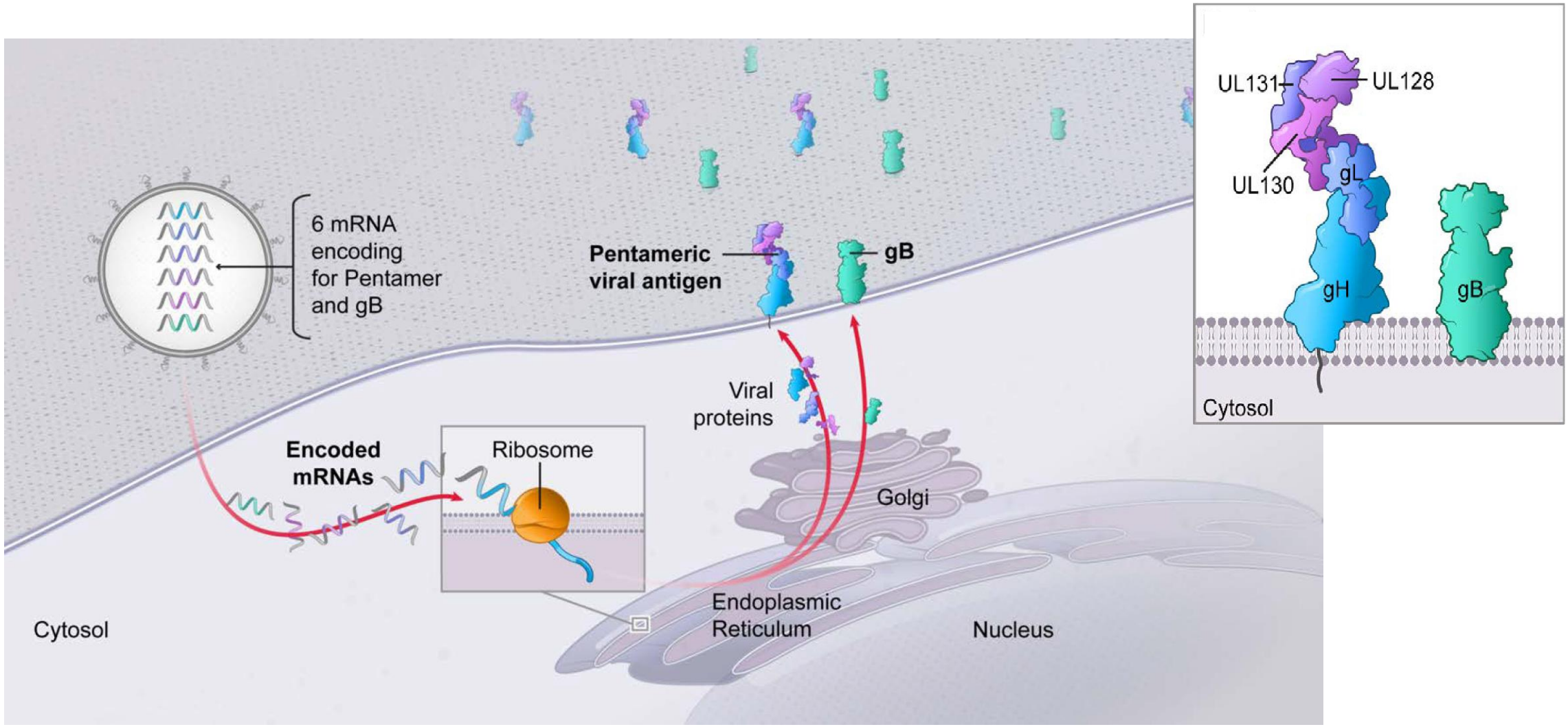
babies in the U.S. are born with a congenital CMV infection (CMV infection is present at birth)

1 in 5

will have severe, life-altering health problems

(1) Grosse, Scott et al. "Economic assessments of the burden of congenital cytomegalovirus infection and the cost-effectiveness of prevention strategies," *Seminars in perinatology,* 2021, https://doi.org/10.1016/j.semperi.2021.151393

CMV vaccine comprises six mRNAs encoding the CMV pentamer complex and gB antigens together

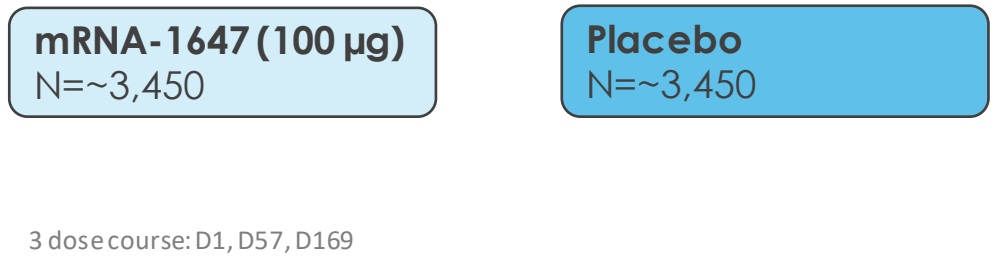


CMV vaccine (mRNA-1647) Phase 3 trial is >40% enrolled

- Randomized, observer-blind, placebo-controlled study to evaluate the **efficacy, safety and immunogenicity of mRNA-1647 to evaluate prevention of primary infection**
- **Enrollment is ongoing in the U.S. and internationally**
  - Expected to enroll up to 6,900 women of childbearing age
  - Approximately 150 sites globally
- **Participants must be at a higher risk of contracting CMV**
  - Participants aged ≥20 years must anticipate having direct exposure (home, socially or occupationally) to at least 1 child ≤5 years of age
- Goal to **enroll a diverse group of U.S. participants** into the study
- **Primary efficacy analysis will be triggered based on accrual of seroconversion cases**; meeting the primary objective will be the basis for filing

CMVictory

Ph 3 trial design



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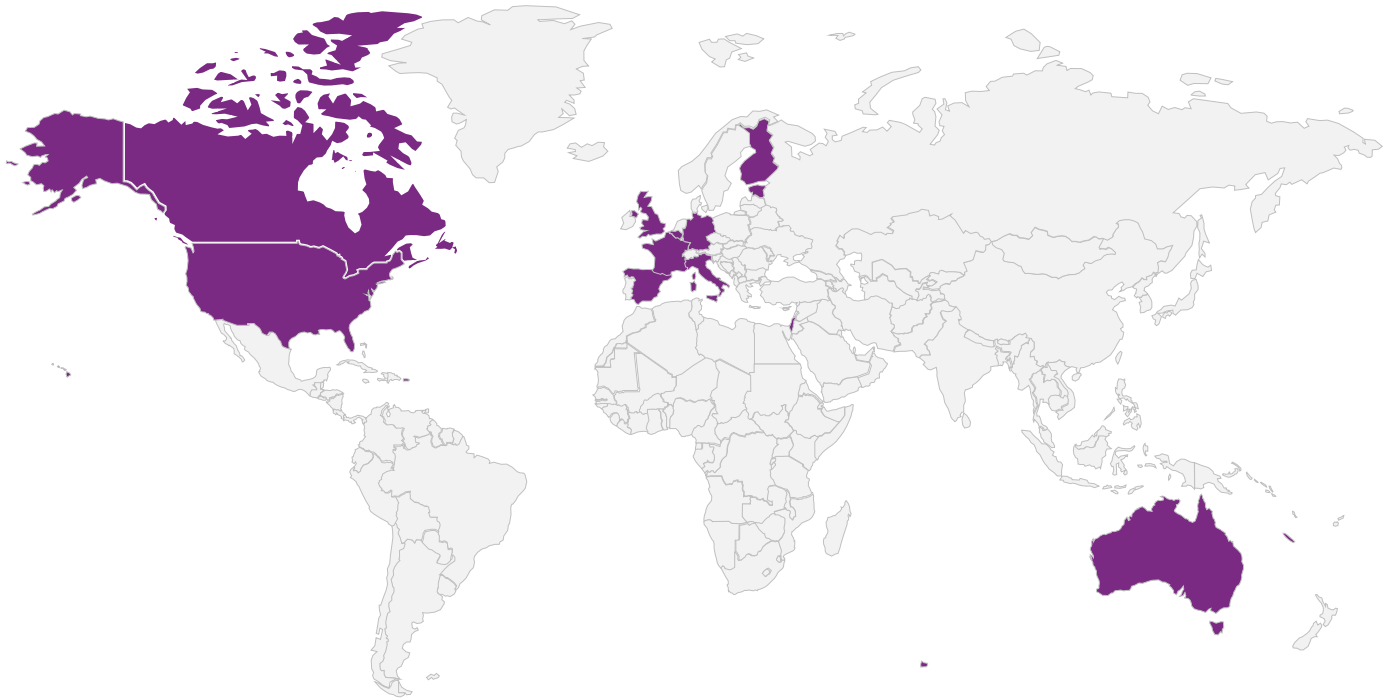
CMV vaccine (mRNA-1647) Phase 3 trial ongoing worldwide

Enrolling in ~150 sites in 12 countries

CMVictory

US Enrollment Targets Based on Demographic Composition

	Target	Current%
White, non-Hispanic	58%	52%
Hispanic/LatinX	23%	33%
Black or African American	12%	11%
Asian	4%	2%
Others	3%	2%
White	**58%**	**52%**
Persons of color	**42%**	**48%**



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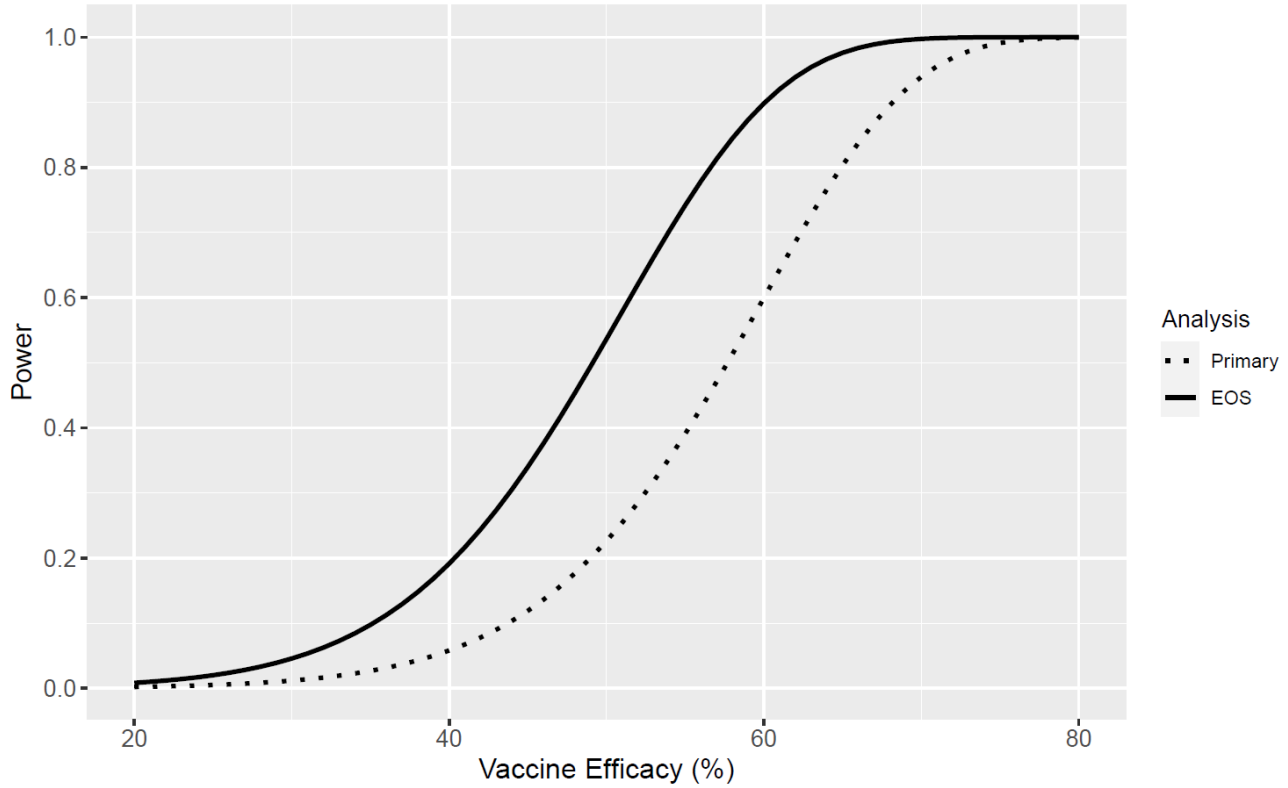
Overview of primary efficacy endpoint

Efficacy Boundaries with Alpha-allocation between 2 Planned Analyses

	Approximate # of Cases	One-sided Alpha	VE: Efficacy Bound
Primary Analysis	81	0.5%	~ 57.7%
End of Study (EOS) Analysis	112	2.0%	~ 49.1%



CMV infection is a frequent complication after transplantation

Infection occurs due to transmission from the transplanted organ, reactivation of latent infection, or after a primary infection in seronegative patients

- **The harmful effects of CMV in transplant recipients result from:**
  - The direct effect of the virus on various organs and systems
    - Mainly causing pneumonia, gastrointestinal tract disease, hepatitis, encephalitis, and retinitis[1]
  - The indirect immunomodulatory effects of the virus
    - Predisposing patients to graft rejection and other opportunistic infections[2]

- In solid organ transplantation (SOT), **the greatest risk factor for CMV disease is a serological mismatch between the donor and the recipient** (the recipient is CMV seronegative and the donor is seropositive)

Incidence of CMV disease risk[3]		
	Donor+/recipient –	Recipient +
Kidney	0-50%	2-15%
Liver	8-40%	0-4%
Lung	10-33%	7-19%
Heart	0-25%	0-14%
	Recipient -	Recipient +
Allogeneic HSCT[4]	0-12%	30-80% (median 37%)

1. Azevedo, Luiz et al., *Clinics (Sao Paulo)* (2015), https://doi.org/10.6061/clinics/2015(07)09
2. Haidar, Ghady et al., *J Infect Dis* (2020), https://doi.org/10.1093/infdis/jiz454
3. Limaye, Ajit et al., *ASMJournals* (2020), https://doi.org/10.1128/CMR.00043-19
4. Styczynski, Jan, *Infect Dis Ther.* (2018)

Investigation of mRNA-1647 in the transplant population

Anticipating trial start-up in late 2022

- **Objective**: Design a proof-of-concept trial or trials to evaluate the safety, efficacy and immunogenicity of mRNA-1647 in allogeneic hematopoietic stem cell transplant recipients and solid organ transplant recipients

- **Design**: Utilize mRNA-1647 as an adjunct to standard of care for the prevention of CMV

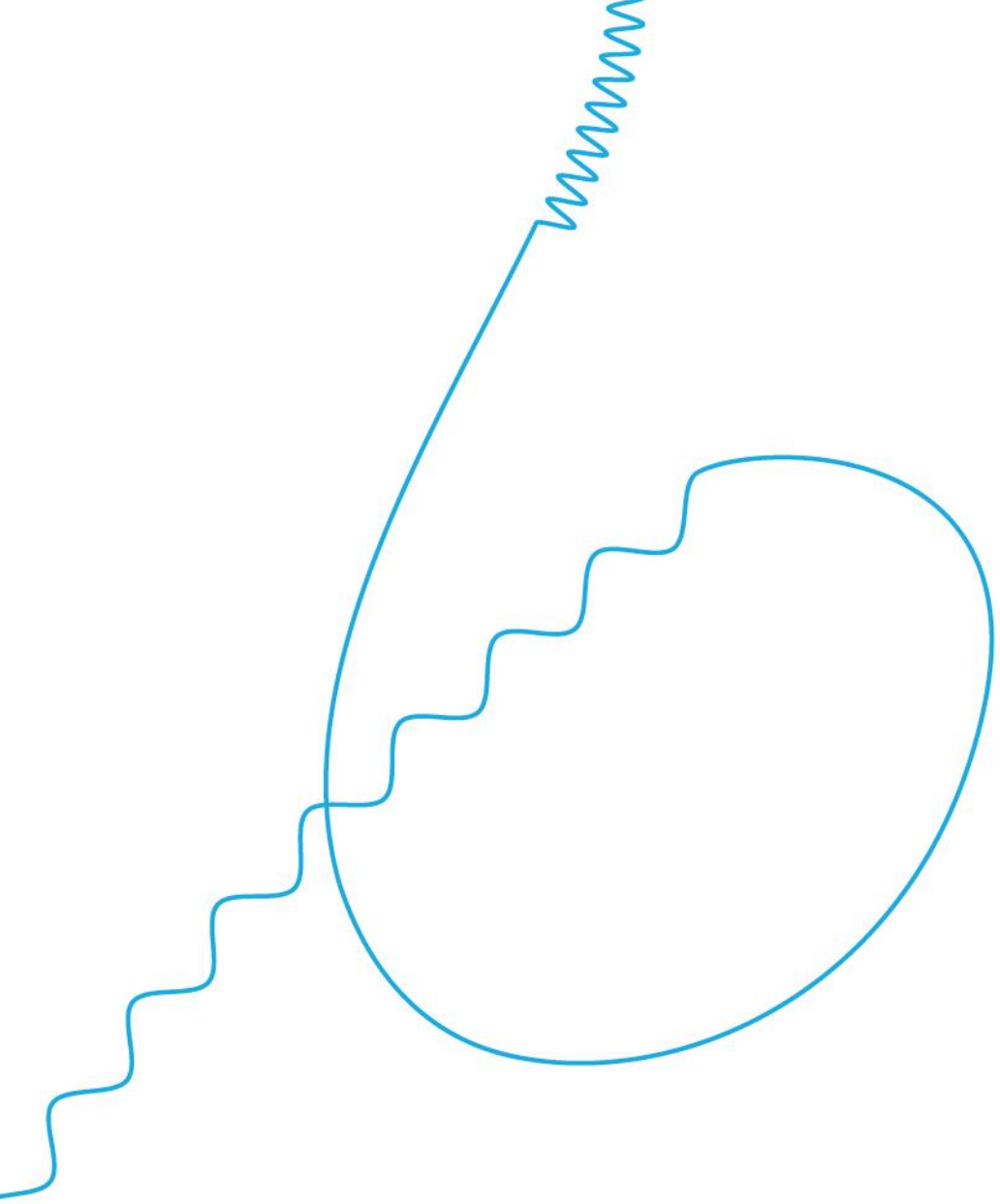
- **Considerations**: Evaluation of mRNA-1647 in a unique immunocompromised population, assessing:
  - Safety
  - Ability of mRNA-1647 to elicit an immune response
  - Durability of the immune response
  - Ability of mRNA-1647 to prevent either CMV reactivation or reinfection
  - Impact of mRNA-1647 on transplant-related and CMV-related outcomes

CMV vaccine (mRNA-1647) is advancing in a pivotal Phase 3 study

CMV is a large unmet need in women of child-bearing age; CMV is also a large healthcare burden in the transplant population and we plan to start a study ev aluating plan to start a study in transplant population

CMVictory trial is >40% enrolled and we are on track to meet D&I targets

Timing of readout depends on **number of CMV cases accrued in study**



Commercial Preparedness

Arpa Garay

Chief Commercial Officer

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Commercial organization strategic priorities

1. Compete in 2023 endemic market
2. Create/expand respiratory vaccine markets (RSV, flu, combos)
3. Educate HCPs and the public about CMV in advance of CMV vaccine launch
4. Gear up for potential launch of therapeutics

Late-stage vaccines and potential launch timing

			Preclinical	Phase 1	Phase 2	Phase 3	Licensed
Respiratory Infectious Diseases	mRNA-1273	SARS-CoV-2					
	mRNA-1010	Seasonal Flu (HA)					Earliest 2023
	mRNA-1345	RSV (older adults)					Earliest 2023
Latent and Public Health Infectious Diseases	mRNA-1647	CMV					Potential 2026

- **COVID boosters**: Launching Omicron-targeting bivalent candidates
- **Flu**: Immunogenicity readout expected in 2023
- **RSV**: Depending on RSV case accrual, efficacy could readout in 2023
- **CMV**: Depending on enrollment and CMV infection accrual, earliest efficacy could readout in 2024-2025

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Transitioning to an endemic COVID market

Pandemic context

Nationalized country vaccine procurement, including a single point of contact for all EU sales

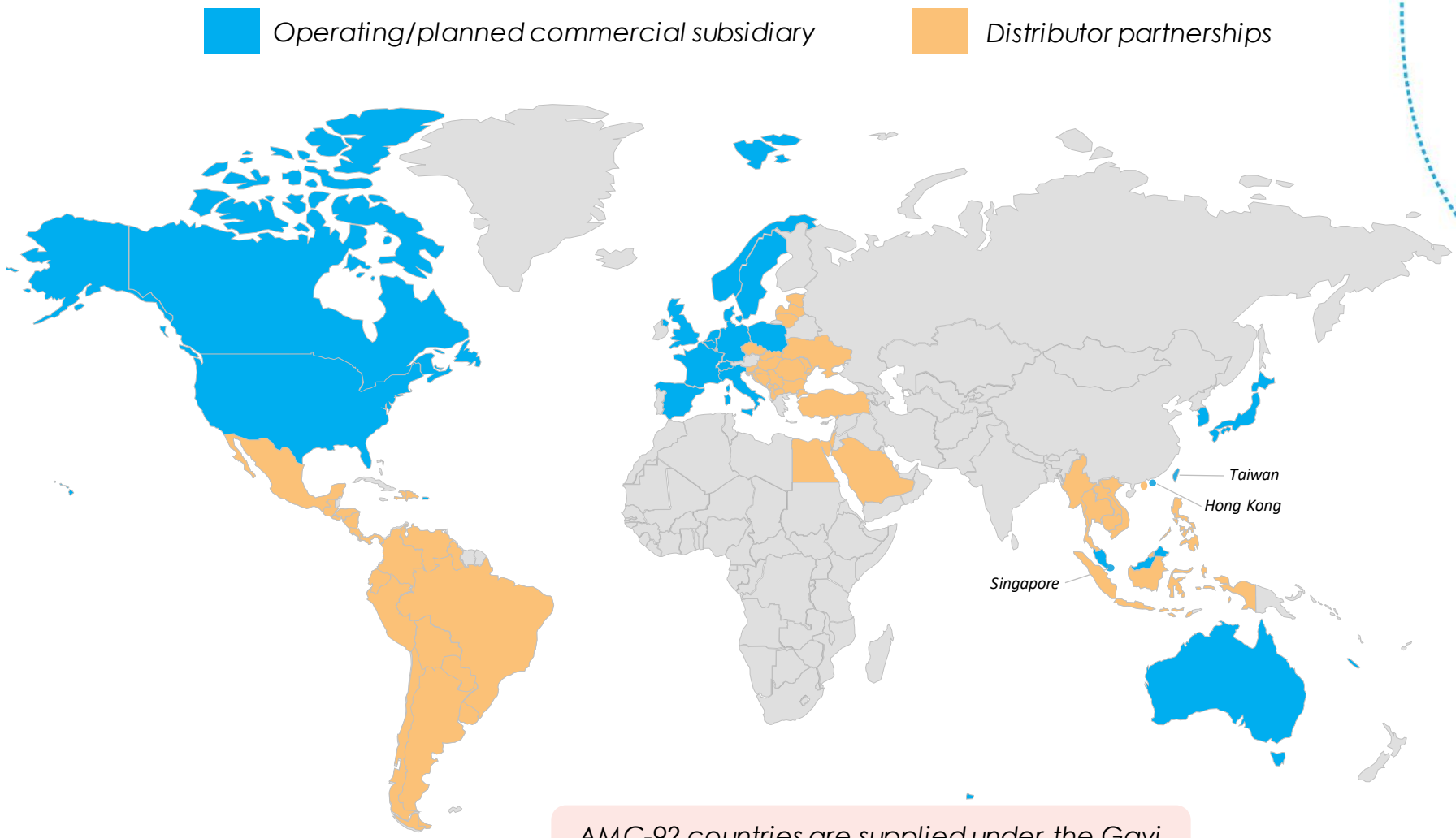
Accelerated regulatory review (product approvals, labeling, packaging, CMO site qualification …)

Endemic market

- More **fragmented commercial model; in U.S.:**
  - USG buys for Medicare, Medicaid
  - Private insurance health plans (UNH, Cigna, Blue Cross)
  - Private commercial market: Development of commercial market to large employers
- **EU countries procuring individually**
  - A variety of commercial models in EU countries (tender, national procurement, regional procurement) requiring different capabilities
- **Flu market could be a proxy for seasonality of sales:** Commercial process for fall season usually starts in December of the preceding year
  - Orders are typically completed by end of Q1, but additional orders can be made throughout year
  - Manufacturing timelines, competition and previous seasons are factors for sales timing

Endemic market dynamics: global sales infrastructure

- Moderna has **direct presence in almost all major markets** where respiratory vaccines have high utilization/sales
  - 91% of the flu market
  - 87% of the pneumococcal vaccine market[1]



AMC-92 countries are supplied under the Gavi Agreement, with UNICEF / PAHO support

1. IQVIA market data

The respiratory vaccines market is substantial, and could be even larger with new, improved solutions

How does COVID change the respiratory vaccines market?

- Recognition of vaccines as the gold standard in preventing disease burden and medical costs
- Increased awareness of mRNA vaccine efficacy
- Economic and social disruption from pandemic
- Recommendations for broader age groups[1]

1. CDC Recommends the First Updated COVID-19 Booster, https://www.cdc.gov/media/releases/2022/s0901-covid-19-booster.html

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Endemic COVID market: Opportunity to expand from high-risk population

COVID market

- Recent pandemic COVID vaccines market **>$100 billion**[1]
- In high-income countries, the **eligible high-risk population is ~340 million**
  - High-risk population due to age 65+ and adults 50-65 with at least one risk factor[2]

Potential U.S. COVID market (high-risk population only and all adults)

COVID vaccine price assumptions	$64	$82	$100
High-risk population in U.S. (~82M) only	$5.2B	$6.7B	$8.2B
All adults (18+ yrs) population in U.S. (~258M) @ 50% coverage rate	$8.3B	$10.6B	$12.9B

- **U.S. flu vaccine coverage ratio in all adults (18+ yrs) is ~50%**[3]; generally lower in other high-income countries
- Recent Centers for Medicare & Medicaid Services (CMS) **price for CY22/23 was $64**[4]

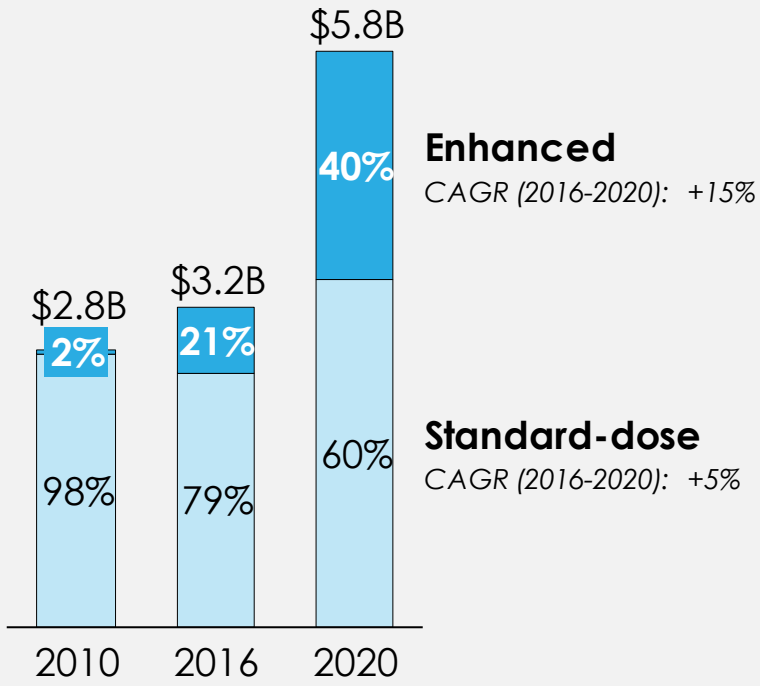
(1) Reported and expected vaccine sales
(2) CDC, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html#print; Ajufo, Ezimamaka et al., *The American Journal of Cardiology* (2021), https://doi.org/10.1016/j.ajpc.2021.100156; Clark, Andrew et al., *Lancet Glob Health* (2020), https://doi.org/10.1016/S2214-109X(20)30264-3
(3) CDC, https://www.cdc.gov/flu/fluvaxview/coverage-2021estimates.htm
(4) CMS, https://www.cms.gov/files/document/2023-announcement.pdf
Population numbers from U.S. Census

Flu market: Opportunity to expand the market with premium vaccines

Flu market	Market dynamics	
Current influenza market $5-6+ billion		
Market could grow even larger with better, more effective vaccines	**Addressable population**	• Aim for recommendation in older adults (>65 years old) • Adults 18+ eligible • Explore pediatric indications
	Enhanced vaccines	• Premium vaccines with improved vaccine efficacy get a higher price (>$50/dose) and are growing at a faster rate[2]

Reported Global Influenza Vaccine Sales[1]

USD, billions



Note: Source: EvaluatePharma, IQVIA MIDAS, Sanofi Vaccine Day (2021); High-dose products include Fluzone HD, Flublok, Fluad, total sales estimated

1. EvaluatePharma, IQVIA MIDAS, Sanofi Vaccine Day (2021); High-dose products include Fluzone HD, Flublok, Fluad, total sales estimated
2. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/VaccinesPricing

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Older adults RSV market is a >$10 billion market

RSV market	Market dynamics	
RSV market has the potential to be >$10 billion market[1]	**Addressable population**	• Older adults (>65 years old) • Pediatric trials ongoing
	Market share	• Depends on efficacy readout compared to other late-stage competitors
	Price	• Innovative, best-in-class vaccines have pricing power

1. Analyst reports, FiercePharma

Adult combination vaccines have the potential to transform the vaccine market

Benefits of combination vaccines

- Higher **compliance**
- Better **uptake**
- Larger **benefit to healthcare system**
  - Administration cost for a vaccine can be $40 per shot[1]
- Consumer **convenience**

1. CMS, https://www.cms.gov/files/document/2023-announcement.pdf

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Vaccines for latent viruses have different market dynamics when compared to respiratory vaccines

- **Latent viruses** (such as herpes viruses and HIV) **do not follow seasonal patterns**
- **Demand is more constant over time**, and market increases by expanding eligible populations (such as going down in age)
- **Innovative vaccines can grow to multi-billion businesses**
  - Gardasil: >$5B revenue in 2021; price is $250 per course[1]
  - Shingrix: >$2B revenue in 2021; price is $340 per course[2]

CMV market

CMV is a $2-5 billion opportunity

- Build and expand the CMV market
  - Older adolescents/women of child-bearing age (4 million births a year in the U.S.)
  - Toddlers
- New indications
  - CMV transplant population

1. Revenue: Evaluate Pharma estimates; Price
2. Revenue: Evaluate Pharma estimates; Price

Rare disease marketing dynamics

			Preclinical	Phase 1	Phase 2	Phase 3	Licensed
Rare Diseases	mRNA-3927	PA					Earliest 2024
	mRNA-3705	MMA					Earliest 2024
	mRNA-3745	GSD1a					TBD

- **Unique regulatory benefits:** High unmet need allows for accelerated timelines with regulators
- **KOLs:** Limited exposure to patients with rare disease require more education to diagnose and treat; concentrated base of patients through patient advocacy group
- **Increased awareness drives diagnosis:** Epidemiology estimates often understated for rare diseases without treatment options
- **Other unique factors of rare disease:** Additional benefits from Orphan Drug Designation (ODD)

Commercial preparedness summary

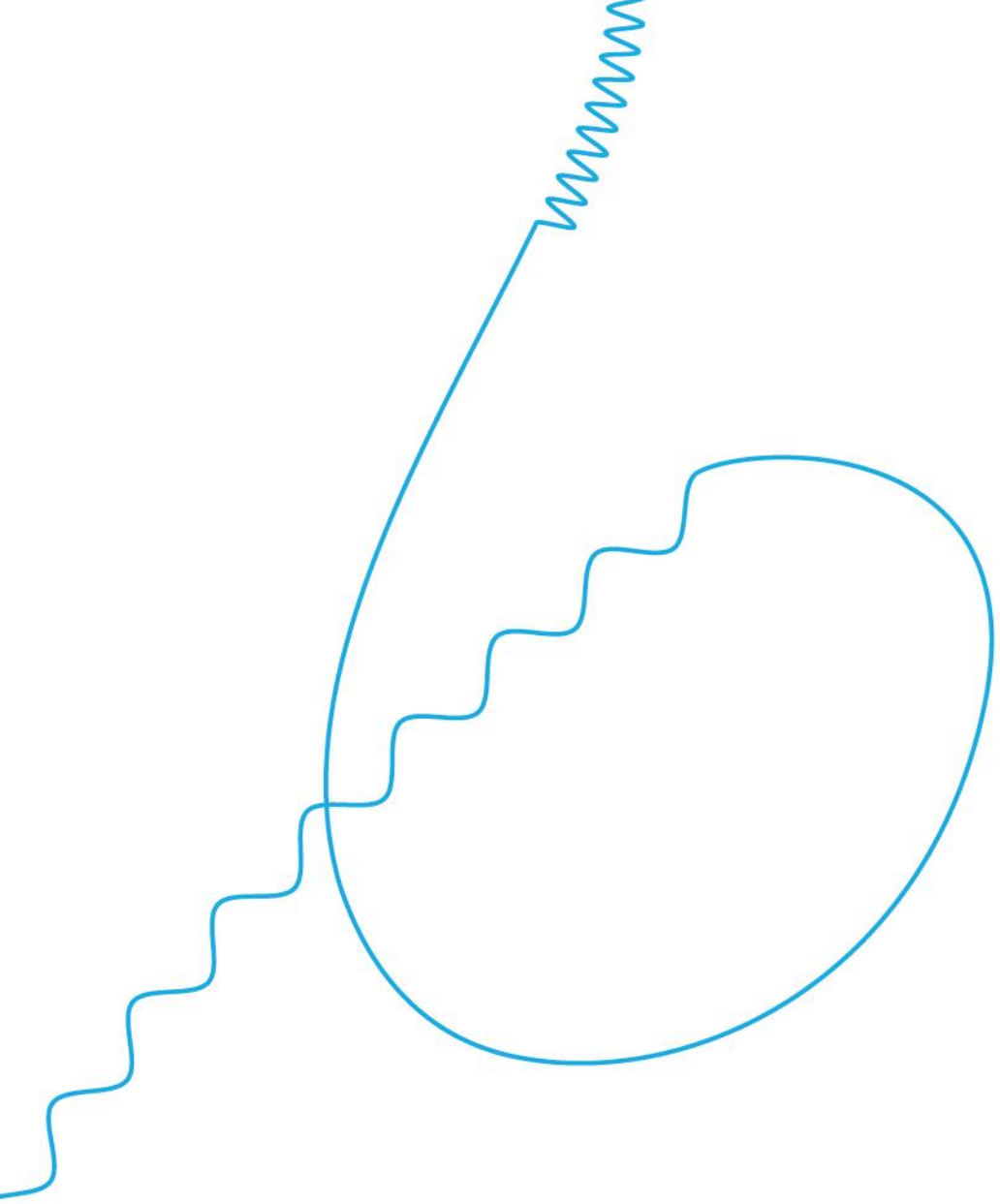
We have the **global scale** to compete in the COVID endemic market

Preparing for **multiple vaccine** launches between 2023-2026

Respiratory vaccines markets are **large, multi-billion-dollar opportunities** and combination vaccines provide **competitive advantages**

Latent virus vaccines have different market dynamics and **CMV offers a >$2 billion market opportunity**

mRNA therapeutics in rare diseases can move quickly given regulatory pathway and motivated population



Conclusion

Stéphane Bancel

CEO

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Never been as optimistic

Last 10 years

- We believed mRNA might work
- Capital constrained

2022

- We know mRNA can work safely
- Unique balance sheet for a 10-year-old biotech (~$18B)

The next 2-3 quarters are going to be really interesting

Select catalysts

- **PA & GSD1a** showing encouraging data
  - Could see a pivotal study in PA start in 2023 (MDEs)
  - De-risks our rare liver disease programs
- **PCV** Phase 2 data in 4Q22
- **Flu** Phase 3 data in 1Q23
- **RSV** Phase 3 data could readout this winter

Moderna has been built to create a lot of optionality

- **Flu** Phase 3
- **RSV** Phase 3
- **PCV** Phase 2
- **PA** enabling the rare disease portfolio
- **CF** (can we deliver mRNA into the lung)
- **More vaccines** (coming from the Moderna Infectious Disease lab)
- **Gene editing**
- Expansion of the Moderna mRNA platform to enable **new families of drugs**

Thank you

Collaborators, investigators and patients and their families…!

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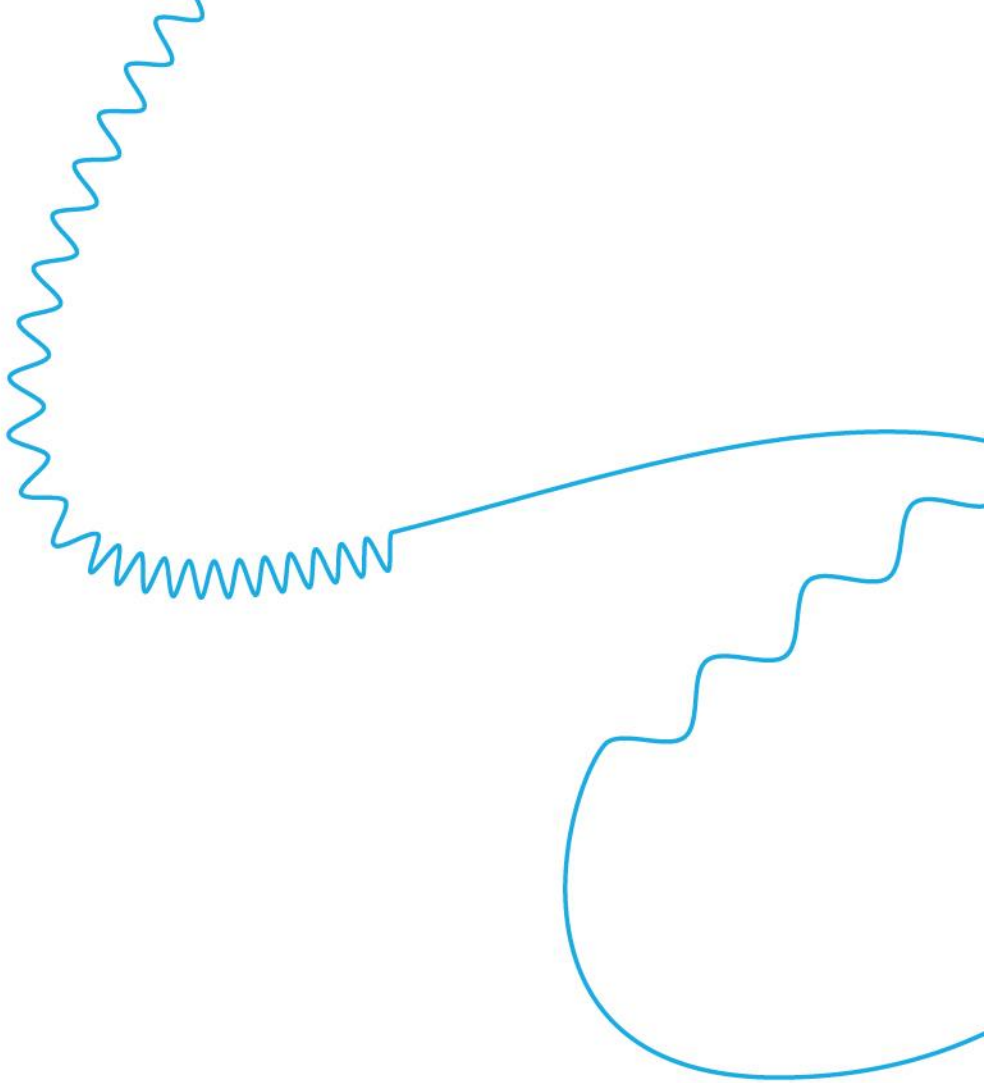
Our mission

To deliver on the promise of mRNA science to create a new generation of transformative medicines for patients.

Q&A



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