BEFORE THE
SCIENCE COMMITTEE OF THE
INDEPENDENT CITIZENS' OVERSIGHT COMMITTEE
TO THE
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
ORGANIZED PURSUANT TO THE
CALIFORNIA STEM CELL RESEARCH AND CURES ACT

REGULAR MEETING

LOCATION: VIA ZOOM

DATE: JANUARY 14, 2026
12:30 P.M.

REPORTER: BETH C. DRAIN, CA CSR
CSR. NO. 7152

FILE NO.: 2026-2

I N D E X

JANUARY 14, 2026; 12:30 P.M.

CHAIRMAN FISCHER-COLBRIE: GREAT. LET'S CALL TO ORDER THE SCIENCE SUBCOMMITTEE AND WOULD LIKE TO HAVE SCOTT CALL THE ROLL.

MR. TOCHER: MARIA BONNEVILLE.

VICE CHAIR BONNEVILLE: PRESENT.

MR. TOCHER: DEBORAH DEAS. MARK FISCHER-COLBRIE.

CHAIRMAN FISCHER-COLBRIE: HERE.

MR. TOCHER: ELENA FLOWERS.

DR. FLOWERS: PRESENT.

MR. TOCHER: JUDY GASSON. STEVE SMALE FOR JUDY GASSON.

DR. SMALE: HERE.

MR. TOCHER: VITO IMBASCIANI.

CHAIRMAN IMBASCIANI: HERE.

MR. TOCHER: PAT LEVITT.

DR. LEVITT: HERE.

MR. TOCHER: SHLOMO MELMED.

DR. MELMED: HERE.

MR. TOCHER: CAROLYN MELTZER.

DR. MELTZER: PRESENT.

MR. TOCHER: CHRIS MIASKOWSKI.

DR. MIASKOWSKI: PRESENT.

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MR. TOCHER: SHAUNA STARK.

DR. STARK: PRESENT.

MR. TOCHER: KAROL WATSON.

DR. WATSON: HERE.

MR. TOCHER: KEITH YAMAMOTO.

DR. YAMAMOTO: HERE.

MR. TOCHER: GREAT. THANK YOU VERY MUCH, KEITH. GREAT. WE HAVE A QUORUM. MARK.

CHAIRMAN FISCHER-COLBRIE: GREAT. THANK YOU SO MUCH. AND FIRST ORDER OF BUSINESS IS DR. SHYAM PATEL WILL PRESENT INFORMATION AND A PROPOSAL WITH RESPECT TO THE RAPID PROGRAM. SO, SHYAM, IF YOU'D LIKE TO TAKE OVER THE MEETING AND RESPOND TO QUESTIONS AS THEY COME UP, THAT WOULD BE GREAT.

DR. PATEL: GREAT. THANK YOU, MARK. I'M GOING TO SHARE MY SCREEN. HOPEFULLY EVERYONE CAN HEAR ME AND CAN SEE THE PRESENTATION. SO THANK YOU TO THE SCIENCE SUBCOMMITTEE CO-CHAIRS AND THE SCIENCE SUBCOMMITTEE FOR THE OPPORTUNITY TO PRESENT TO YOU TODAY.

I'M GOING TO BE PRESENTING THE RAPID FUNDING OPPORTUNITY ON BEHALF OF MY TEAMMATES, DR. JIM CAPANELLI AND DR. LISA MCGINLEY. AND THE RAPID FUNDING PROGRAM STANDS FOR RARE DISEASE

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ACCELERATION THROUGH PLATFORM INNOVATION AND DELIVERY.

SO I'LL START OFF WITH THE IMPACT GOAL AND THEN A SIGNIFICANT AMOUNT OF BACKGROUND ON WHY THIS INITIATIVE IS NECESSARY AND WHAT THE LANDSCAPE IS ENTERING INTO. AND THEN I'LL FOLLOW THAT UP WITH TALKING ABOUT THE ACTUAL FUNDING PROGRAM AND THE MECHANICS AND STRUCTURE OF THE AWARDS.

SO THE RAPID FUNDING OPPORTUNITY IS RESPONSIVE TO THE SAF GOAL 3, WHICH WAS TO ADVANCE FOUR TO SEVEN RARE DISEASE PROJECTS TO BLA. AND IN THAT IS ADDRESSING THE SITING RECOMMENDATION THAT WAS MADE TO THE BOARD, WHICH IS TO PILOT PLATFORM-BASED THERAPY DEVELOPMENT FOR GENE THERAPY. AND THIS IS TO CREATE A NEW MODEL FOR HOW TO ACCELERATE GENE THERAPY DEVELOPMENT FOR RARE DISEASES.

SO AS MANY OF YOU KNOW, THERE ARE AT LEAST 10,000 UNIQUE RARE DISEASES IN THE PATIENT POPULATION TODAY. COLLECTIVELY THEY AFFECT OVER 30 MILLION PEOPLE IN THE U.S. SO EACH RARE DISEASE MAY HAVE A SMALL POPULATION, BUT CUMULATIVELY THEY AFFECT OVER 30 MILLION PEOPLE. 50 PERCENT OF THESE RARE DISEASES ARE CHILDHOOD DISEASES AND 80 PERCENT HAVE A GENETIC BASIS.

AND DESPITE THE VAST MAJORITY OF CELL AND GENE THERAPIES THAT HAVE BEEN APPROVED TO DATE HAVE BEEN TARGETING RARE DISEASES, 95 PERCENT OF RARE DISEASES HAVE NO APPROVED THERAPY. AND THIS IS DUE TO THE FACT THAT THE TRADITIONAL DRUG DEVELOPMENT PATHWAY IS SLOW, EXPENSIVE, AND DOESN'T REALLY ALLOW FOR MASS DEVELOPMENT AND PRODUCTION OF GENETIC THERAPIES FOR THE LARGE NUMBER OF RARE DISEASES THAT ARE AFFECTING THE POPULATION.

SO THIS SLIDE DESCRIBES BRIEFLY WHAT THE THERAPEUTIC DEVELOPMENT PATHWAY LOOKS LIKE. YOU'VE SEEN THIS IN VARIOUS DIFFERENT FLAVORS. ALTHOUGH GENETIC THERAPIES ENJOY A RELATIVELY FASTER TIMELINE THAN TRADITIONAL SMALL MOLECULES AND BIOLOGICS, IT STILL TAKES 10 TO 20 YEARS TO GO FROM THE FULL DEVELOPMENT LIFE CYCLE OF CANDIDATE DISCOVERY THROUGH APPROVAL FOR THESE THERAPIES. AND BECAUSE THE DEVELOPMENT OF EVERY SINGLE GENE THERAPY IS SO TIME, COST, AND RESOURCE INTENSIVE, IT REALLY IS VERY DIFFICULT TO DEVELOP GENETIC THERAPIES IN A MULTIPLEX MANNER. YOU'RE BASICALLY DEVELOPING EACH THERAPY ONE AT A TIME. AND WE OFTEN SEE THESE TYPES OF PROGRESSION PLOTS FOR COMPANIES AND ACADEMICS WHERE THEY SHOW ONE THERAPY BEING DEVELOPED AT A TIME IN A STAGGERED WAY.

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SO THERE HAS TO BE A BETTER WAY. WHAT IF THE DEVELOPMENT TIMELINE IS ACCELERATED? WHAT IF WE DEVELOPED DRUGS FASTER? SO THIS WAS RECENTLY EXEMPLIFIED BY THE CHILDREN'S HOSPITAL OF PHILADELPHIA'S EXPERIMENT WITH BABY KJ'S GENE EDITING THERAPY WHERE THEY WERE ABLE TO DEVELOP AND ADMINISTER WITHIN SIX MONTHS OF DIAGNOSIS THE GENETIC THERAPY FOR BABY KJ'S UREA CYCLE DISORDER.

HOWEVER, IN DEVELOPING THIS THERAPY, THEY HAD TO LARGELY DO ALL OF THE TESTING THAT YOU WOULD DO FOR A GENE THERAPY. SO THIS INCLUDED MULTIPLE ANIMAL MODELS, INCLUDING MOUSE AND NHP MODELS, AND ALL OF THE MANUFACTURING ASSOCIATED WITH THAT. SO WHILE THE TIMELINE WAS CONDENSED, IT WAS STILL VERY COSTLY AND RESOURCE INTENSIVE PROCESS TO DEVELOP THIS THERAPY WITHIN A SIX-MONTH TIME FRAME.

AND SINCE THIS N OF 1 THERAPY WAS DEVELOPED FOR A SINGLE PATIENT AND TESTED FOR A SINGLE PATIENT, THE NEXT BABY KJ WOULD REQUIRE THE ENTIRE PROCESS TO BE REPEATED.

SO I'M GOING TO TAKE A QUICK PAUSE HERE AND GO BACK TO A PREVIOUS SLIDE, AND I'M GOING TO MAKE AN ANALOGY TO CARS. AND SO I DRIVE A VERY UTILITARIAN HONDA CRV, AND I'M GOING TO COMPARE THAT TO A HONDA CIVIC, A SEDAN. SO YOU'VE GOT A CRV,

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WHICH IS AN SUV, AND A SEDAN, WHICH IS THE HONDA CIVIC. NOW, ON THE FACE OF IT, THEY LOOK LIKE TWO COMPLETELY DIFFERENT CARS WITH DIFFERENT FUNCTIONS AND DIFFERENT LIFESTYLES THAT THEY WOULD BE TAILORED TO. HOWEVER, THEY'RE ACTUALLY BASED ON THE SAME PLATFORM. SO THE CRV WAS DESIGNED AND TESTED AND MANUFACTURED ON THE CIVIC PLATFORM, AND EVERY SUCCESSIVE GENERATION IS BUILT ON THE CIVIC PLATFORM AS WELL. THIS WAS A DELIBERATE STRATEGY TO LEVERAGE PLATFORM EFFICIENCIES FOR DESIGN, DEVELOPMENT, TESTING, AS WELL AS MANUFACTURING AND MAINTENANCE OF THESE TWO MODELS OF CARS FOR EVERY GENERATION.

SO WHAT IF FOR DRUG DEVELOPMENT YOU WERE ABLE TO LEVERAGE TO THE FULL POTENTIAL ALL OF THE PLATFORM EFFICIENCIES FROM DISCOVERY TO DEVELOPMENT TO CLINICAL TESTING TO APPROVAL? AND THAT'S THE BASIS OF WHAT CONSTITUTES THIS CONCEPT OF PLATFORM-BASED THERAPIES.

SO HERE MULTIPLE RELATED THERAPIES FOR MULTIPLE INDICATIONS ARE RAPIDLY ADVANCED TO PATIENTS BY LEVERAGING COMMON COMPONENTS, TECHNOLOGIES, DATA, AND RESOURCES. SO THIS SLIDE ILLUSTRATES THREE POTENTIAL GENETIC THERAPIES THAT ARE PLATFORMIZABLE. THIS INCLUDES NONVIRAL GENE EDITING, RNA-BASED THERAPIES, AND AAV GENE DELIVERY.

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NOW, IF WE LOOK AT THE GENE EDITING CRISPR TECHNOLOGY IN PARTICULAR, CRISPR HAS REVOLUTIONIZED MEDICINE BECAUSE IN A WAY IT MAKES IT REALLY EASY TO DISCOVER A LARGE NUMBER OF CANDIDATES FOR MULTIPLE MUTATIONS. AND THE REASON FOR THIS IS BECAUSE THE MACHINERY FOR CRISPR OR GENE EDITING INCLUDES AN EDITOR, WHICH IS GOING TO DO THE MODIFICATION TO THE DNA, A GUIDE RNA WHICH DIRECTS THE EDITORS TO THE APPROPRIATE GENETIC SEQUENCE, AND A DELIVERY VEHICLE, LIKE AN LNP. SO IN THAT INSTANCE, YOU CAN GENERATE A LARGE NUMBER OF DIFFERENT CANDIDATES RAPIDLY BY ITERATING JUST ON THE GUIDE RNA.

HOWEVER, WHERE THE CHALLENGE LIES IS HOW YOU EXTEND THAT PLATFORM EFFICIENCY FROM JUST DRUG DISCOVERY TO DEVELOPMENT, PRECLINICAL DEVELOPMENT, CLINICAL TRIALS, AND APPROVAL. AND SO ON THE NEXT SLIDE I'M GOING TO DEMONSTRATE THE VISION FOR PLATFORM EFFICIENCIES WHERE YOU CAN LEVERAGE IT ACROSS THE ENTIRE LIFE CYCLE FOR DRUG DEVELOPMENT.

SO I'M GOING TO GO BACK TO THE BABY KJ EXAMPLE. SO BABY KJ HAS A UREA CYCLE DISORDER WHICH AFFECTS ONE PARTICULAR GENE. HOWEVER, THERE ARE SIX OTHER GENES WHERE A MUTATION IN ANY ONE OF THOSE GENES CAN RESULT IN THE SAME TYPE OF DISEASE WITH SIMILAR PATHOLOGY. AND SO WHAT IF YOU WERE TO

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DEVELOP GENETIC THERAPIES FOR ALL SEVEN GENES AT THE SAME TIME IN PARALLEL? AND THAT'S WHAT THIS PARTICULAR SLIDE IS GOING TO ENCAPSULATE.

SO FIRST OF ALL, AS I ALREADY MENTIONED, YOU CAN RAPIDLY IDENTIFY THERAPIES FOR ALL SEVEN MUTATIONS IN THIS SIMPLIFIED EXAMPLE BY JUST CHANGING THE GUIDE RNA SEQUENCE.

NEXT, AT THE PRECLINICAL STAGE, IF YOU RESERVE THE BULK OF THE TESTING ON A SINGLE CANDIDATE, SO YOU DO ALL OF YOUR ANIMAL TESTING, ALL OF YOUR SAFETY AND EFFICACY TESTING, ON A SINGLE CANDIDATE AND YOU RESERVE IN VITRO TESTING FOR THE REST OF THE CANDIDATES, YOU COULD REALIZE A LOT OF EFFICIENCY AT THE PRECLINICAL STAGE.

AND, IN FACT, THIS APPLIES TO MANUFACTURING AS WELL WHERE, IF YOU HAVE SIMILAR COMPONENTS LIKE THE LIPID NANOPARTICLE AND EDITOR, BY MANUFACTURING AT SCALE ACROSS ALL SEVEN CANDIDATES, YOU CAN REALIZE THAT EFFICIENCY AS WELL.

THE NEXT STEP WOULD BE TO, INSTEAD OF DOING A SINGLE CLINICAL TRIAL FOR EVERY SINGLE CANDIDATE DRIVEN BY ITS OWN IND, IS TO SUBMIT A MASTER PROTOCOL IND TO THE FDA. AND THE FDA WILL ALLOW YOU TO CONDUCT AN UMBRELLA TRIAL WHERE YOU CAN STUDY ALL SEVEN OF THOSE CANDIDATES AT THE SAME TIME

IN THE SAME TRIAL WHILE ALSO BEING ABLE TO ADD NEW CANDIDATES FOR NEW MUTATIONS THAT MAY ARISE IN THAT PATIENT POPULATION.

FINALLY, INSTEAD OF SUBMITTING EVERY SINGLE CANDIDATE TO THE FDA FOR APPROVAL, WHAT IF THE FDA ALLOWED YOU TO GET PLATFORM-BASED APPROVAL FOR THE ENTIRE PLATFORM BASED ON THE TOTALITY OF THE DATA YOU'VE GATHERED ACROSS ALL THOSE CANDIDATES? THAT WOULD ALLOW YOU NOT ONLY TO RAPIDLY GET APPROVAL FOR THIS PLATFORM, BUT TO ALSO GET RAPID APPROVAL FOR THE NEXT SET OF THERAPIES THAT ALSO LEVERAGE THAT PLATFORM.

AND SO TO DATE THE THOUGHT WAS THAT TO GET TO THIS VISION FOR PLATFORM-BASED DEVELOPMENT, YOU HAVE TO MAKE INCREMENTAL STEPS TOWARD EFFICIENCIES. FOR EXAMPLE, ELIMINATE ONE ANIMAL STUDY HERE OR REDUCE THE NUMBER OF ANIMAL TESTING IN CERTAIN AREAS, AND BUILD ON THAT BY ITERATING ON EACH STEP OF THE PLATFORM TO GET TO THIS VISION. HOWEVER, THAT HAS CHANGED IN THE LAST YEAR BASED ON SOME EARLY INDICATIONS.

SO FIRST OF ALL, I MENTIONED THE CHOP TEAM WHICH DEVELOPED THE BABY KJ THERAPY. THEY HAD STARTED OFF WITH THIS STRATEGY IN MIND, WHICH WAS TO DEVELOP GENETIC THERAPIES IN PARALLEL FOR ALL SEVEN

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MUTATIONS. AND, IN FACT, THEY'VE GONE TO THE FDA AND GOTTEN PRE-IND FEEDBACK TO EXECUTE ON THIS SPECIFIC PLATFORM STRATEGY, WHICH IS TO REALIZE ALL THE EFFICIENCIES AT THE PRECLINICAL TESTING STAGE AND TO DO AN UMBRELLA CLINICAL TRIAL FOR ALL SEVEN GENES AT THE SAME TIME.

IN ADDITION TO THAT, A FEW MONTHS AGO THE FDA, INSPIRED BY, IN PART, THE BABY KJ EXAMPLE, ISSUED A PUBLICATION WHERE THEY DESCRIBED THE PLAUSIBLE MECHANISM PATHWAY. THIS PATHWAY IS MEANT TO DRAMATICALLY ACCELERATE DEVELOPMENT AS WELL AS APPROVAL FOR PLATFORM-BASED GENETIC THERAPIES FOR RARE DISEASES. SO WHILE A LOT NEEDS TO STILL BE DONE IN TERMS OF PROVING THIS PLATFORM APPROACH CAN BE DONE MULTIPLE TIMES WITH DIFFERENT TYPES OF CANDIDATES AND DIFFERENT INDICATIONS, TO DEMONSTRATE CLINICAL PROOF OF CONCEPT AS WELL, AT THIS POINT IN TIME THERE'S A CLEAR FEEDBACK LOOP BETWEEN THERAPY DEVELOPERS AS WELL AS REGULATORS ON HOW TO ADVANCE PLATFORM-BASED GENETIC THERAPY DEVELOPMENT FOR THE VAST NUMBER OF GENETIC DISEASES THAT AFFECT THE CURRENT HUMAN POPULATION.

SO I'M GOING TO TAKE A STEP BACK AND TALK ABOUT HOW WE GOT HERE IN THE LAST YEAR WITH RESPECT TO THE CHOP ADVANCEMENTS AS WELL AS THE FDA

RECEPTIVITY TO THESE APPROACHES. SO ALL THE WORK THAT THE CHOP TEAM DID WITH RESPECT TO BABY KJ AS WELL AS THE BROADER PLATFORM-BASED STRATEGY IS ENABLED BY A SET OF VISIONARY FUNDING OPPORTUNITIES THAT THE NIH LAUNCHED THREE YEARS AGO. THEY HAD A VERY SIMPLE ASK FOR PROPOSALS, WHICH WAS TO BRING TO THEM AN EFFICIENT WAY OF DEVELOPING MULTIPLE GENETIC THERAPIES FOR MULTIPLE DISEASES.

AT THE SAME TIME, AROUND 2024, THE FDA ISSUED PLATFORM DESIGNATION DRAFT GUIDANCE. THIS IS BASED ON REQUIREMENTS OF THE 21ST CENTURY CURES ACT. HOWEVER, THAT PLATFORM DESIGNATION IS NOT ENTIRELY USEFUL FOR GENETIC THERAPY DEVELOPERS BECAUSE IT REQUIRES YOU TO HAVE AN APPROVED PRODUCT IN THE FIRST PLACE. SO THAT SPURRED A LOT OF DIRECT ENGAGEMENT BETWEEN THERAPY DEVELOPERS, PATIENT ADVOCACY ORGANIZATIONS, AND THE GENERAL PUBLIC WITH THE FDA IN VARIOUS DIFFERENT FORMS, WHICH BY AND LARGE INFORMED THE PLAUSIBLE MECHANISM PATHWAY.

SO AT THIS POINT IN TIME, THE RAPID FUNDING OPPORTUNITY IS POSITIONED TO ADVANCE PLATFORM-BASED THERAPIES FROM PROMISE TO PRACTICE BY BUILDING ROBUST EVIDENCE ACROSS RARE DISEASES AND TECHNOLOGIES FOR THIS TYPE OF PLATFORM-BASED APPROACH, TO REALLY GO FORWARD WITH MULTIPLE

THERAPIES FOR MULTIPLE INDICATIONS WHERE YOU REALIZE PLATFORM EFFICIENCIES AT EVERY STEP OF THE DEVELOPMENT PROCESS.

SO IN DESIGNING THIS PROGRAM, WE HAD TWO BROAD GOALS. THE FIRST WAS SCIENTIFIC AND REGULATORY INNOVATION AND THE SECOND WAS PATIENT IMPACT. FOR THE FORMER, WHAT WE WANTED TO ACHIEVE WAS THAT BY SUPPORTING MULTIPLE PROJECTS, THAT ALL OF THEM WOULD DEMONSTRATE THAT YOU CAN GET THIS PATHWAY REALIZED FOR MULTIPLE TECHNOLOGIES AND MULTIPLE INDICATIONS AND BUILD AN EVIDENCE BASE FOR GENE THERAPY PLATFORMS THAT OTHERS CAN LEVERAGE.

AT THE SAME TIME ALL OF THIS POTENTIAL IS NOT REALIZED UNLESS YOU CAN DEMONSTRATE IMPACT ON THE ACTUAL PATIENTS WHO SUFFER FROM THESE DISEASES. AND SO THE PROGRAM WOULD HAVE TO ENSURE THAT ANY SUPPORTED THERAPIES WOULD REACH PATIENTS AS QUICKLY AS POSSIBLE AND THAT THEY WOULD BLAZE A PATHWAY FOR OTHERS TO FOLLOW.

SO WITH THAT IN MIND, THE RAPID PROGRAM HAS A SINGLE OBJECTIVE, WHICH IS TO CREATE A SCALABLE MODEL TO RAPIDLY DELIVER TRANSFORMATIVE, PLATFORM-BASED GENETIC THERAPIES TO PATIENTS WITH RARE DISEASE.

SO AS YOU KNOW, WE HAVE A SET OF LEGACY

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PROGRAMS LIKE TRANSLATIONAL AND CLIN1 AS WELL AS NEWER PROGRAMS LIKE PDEV AND CLIN2, ALL WHICH SUPPORT THERAPY DEVELOPMENT BOTH AT THE PRECLINICAL STAGE AND CLINICAL STAGES. THESE PROGRAMS HAVE A VAST PORTFOLIO OF RARE DISEASE PROJECTS, AND THEY'LL CONTINUE TO SUPPORT THOSE GOING FORWARD. HOWEVER, THESE PROGRAMS ARE NOT CURRENTLY DESIGNED TO ACCELERATE INNOVATIVE, HIGH-RISK PLATFORM APPROACHES. WHY IS THAT? BECAUSE THESE PROGRAMS ARE FOCUSED ON THE TRIED AND TRUE WAY OF DEVELOPING DRUGS, WHICH IS TO FOCUS A PROJECT ON A SINGLE CANDIDATE FOR A SINGLE INDICATION THROUGH THE FULL SUITE OF TESTING FOR EVERY ONE OF THOSE PROJECTS, TO CONDUCT A CLINICAL TRIAL FOR A SINGLE CANDIDATE UNDER A SINGLE IND. SO A LOT OF SINGLES THERE.

FOR THIS PROGRAM, THE RAPID PROGRAM, THE INTENT IS TO SUPPORT DEVELOPMENT IN PARALLEL FOR MULTIPLE CANDIDATES, FOR MULTIPLE RELATED INDICATIONS, ALL OF WHICH WOULD FEED INTO A MASTER PROTOCOL TRIAL. AND HERE THE TESTING ON THE NONCLINICAL SIDE WOULD HAVE TO BE OPTIMIZED WHERE MOST OF IT IS BEING DONE FOR A LEAD CANDIDATE AND REDUCED TESTING FOR THE REST OF THOSE CANDIDATES. AND TO ENSURE ALL THIS HAS PATIENT IMPACT IS TO CLEAR AN ACCELERATED PATHWAY TO THE CLINIC FOR THESE

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PROJECTS.

SO IN A NUTSHELL, MOVING AWAY FROM SINGLE CANDIDATES, SINGLE INDICATION, AND SERIAL DEVELOPMENT OF EACH OF THOSE TO PARALLEL DEVELOPMENT OF MULTIPLE CANDIDATES WHERE ALL OF THAT IS MADE EFFICIENT ON THE WORK THAT HAS BEEN DONE SO FAR.

SO WITH THAT IN MIND, WE ENVISION TWO TYPES OF AWARDS FOR THE RAPID PROGRAM. THE FIRST IS WHAT WE CALL VALIDATION AWARDS. THESE AWARDS ARE MEANT TO ACCELERATE THOSE PROJECTS THAT HAVE POSITIVE PRE-IND FEEDBACK FROM THE FDA ON A PLATFORM-BASED STRATEGY. AND THE INTENT OF THIS IS TO ACCELERATE THOSE THERAPIES TO CLINICAL PROOF OF CONCEPT. DEMONSTRATE THAT THE PRECLINICAL EFFICIENCIES RESULT IN CLINICAL SAFETY AND EFFICACY FOR THESE PLATFORM-BASED THERAPIES. AND THAT WILL THEN CREATE A BLUEPRINT FOR OTHERS TO ADVANCE THE SAME TYPES OF APPROACHES.

SO POTENTIAL EXAMPLE PROJECTS, THESE ARE NONLIMITING, COULD BE NONVIRAL LIVER-TARGETED BASED EDITING THERAPIES FOR METABOLIC DISORDERS. THEY COULD BE AAV-BASED GENE THERAPY FOR NEURODEVELOPMENT DISORDERS. AND THE GOAL -- TO ACHIEVE THE PROGRAM OBJECTIVE, THESE AWARDS WOULD DEMONSTRATE THAT YOU CAN REDUCE FROM PROMISE TO PRACTICE THIS

PLATFORM-BASED THERAPY DEVELOPMENT AND THAT YOU CAN DEVELOP AN EVIDENCE BASE OF CLINICAL SAFETY AND EFFICACY FOR THESE THERAPIES. YOU CAN DELIVER THESE THERAPIES TO PATIENTS, AND YOU CAN DEMONSTRATE THEIR SAFETY AND EFFICACY.

SO TO DESCRIBE THE AWARDS IN A LITTLE BIT MORE DETAIL, THE VALIDATION AWARDS WILL SUPPORT IN VIVO GENETIC THERAPIES FOR RARE DISEASES WHERE THE PLATFORM WILL HAVE TO DEMONSTRATE ACCELERATED AND RESOURCE-EFFICIENT DEVELOPMENT. SO THESE WILL BE PROGRAMS WHERE THE APPLICANT HAS ALREADY SECURED FDA FEEDBACK ON THIS PLATFORM-BASED APPROACH, AND THE PROJECT WILL BE FUNDED TO CONDUCT ALL THE IND ENABLING STUDIES, SUBMIT THE MASTER PROTOCOL IND, AND TO CONDUCT THAT MASTER PROTOCOL CLINICAL TRIAL WITH THE EXPECTED OUTCOME THAT THEY WOULD COMPLETE THAT TRIAL FOR AT LEAST THREE CANDIDATES.

THAT WOULD SET THESE PROJECTS UP TO POTENTIALLY TAKE ADVANTAGE OF THE FDA'S PLAUSIBLE MECHANISM PATHWAY, ALLOWS FOR RAPID DEVELOPMENT AS WELL AS RAPID POTENTIAL PLATFORM APPROVAL FOR THESE TYPES OF APPROACHES.

THESE AWARDS WOULD NOT -- THE PA FOR THIS PROGRAM WOULD NOT SPECIFY AN AWARD CAP AND WILL NOT REQUIRE MINIMUM CO-FUNDING. THE REASON FOR THIS IS

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TO PUT THE ONUS ON THE APPLICANT TO DEMONSTRATE A WELL-JUSTIFIED BUDGET THAT REALIZES TIME, COST, AND RESOURCE EFFICIENCIES ACROSS THE ENTIRE SPECTRUM OF PRECLINICAL AND CLINICAL DEVELOPMENT. AND BECAUSE WE ANTICIPATE A VERY BROAD RANGE OF PROJECTS MIGHT BE ELIGIBLE FOR SUCH A PROGRAM, THAT AN AWARD CAP WOULD BE LIMITING AND DIFFICULT TO SPECIFY. LIKE THE PDEV PROGRAM, THIS PROGRAM WOULD BE LIMITED TO CALIFORNIA ORGANIZATIONS ONLY.

THE SECOND TYPE OF AWARD IS A RAPID INNOVATION AWARD. THE MAIN OBJECTIVE FOR THESE AWARDS IS TO PUSH THE BOUNDARIES OF WHAT CONSTITUTES PLATFORMS. SO WE'RE LOOKING HERE FOR INNOVATIVE REGULATORY AND TECHNOLOGY SOLUTIONS THAT COULD EXPAND THE PLATFORM CAPABILITIES AND THAT COULD ALSO EXPAND TO A MUCH BROADER RANGE OF RARE GENETIC DISEASES. AND WE WOULD SUPPORT THESE PROJECTS THROUGH ALL OF THE PRECLINICAL ACTIVITIES TO OBTAIN IND CLEARANCE FOR THAT PLATFORM-BASED APPROACH.

SO SOME EXAMPLES OF INNOVATIVE APPROACHES HERE COULD BE NONVIRAL GENE DELIVERY TECHNOLOGIES FOR CNS DISORDERS. OR IT COULD BE NEXT GENERATION GENE EDITING THERAPIES THAT ALSO INCORPORATE NOVEL IN VITRO MODELS THAT REDUCE THE NEED FOR ANIMAL TESTING. AGAIN, THESE ARE NONLIMITING EXAMPLES JUST

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FOR THE SAKE OF ILLUSTRATION.

THESE AWARDS WILL ADVANCE THE PLATFORM GOALS BY DEMONSTRATING THAT NEXT GENERATION TECHNOLOGIES CAN BE DEVELOPED WITH A PLATFORM APPROACH IN MIND. AND THEY WOULD ALSO DEMONSTRATE AN ADVANCEMENT IN REGULATORY STRATEGIES GOING FORWARD FOR THESE EMERGING PLATFORMS.

I'LL BRIEFLY DESCRIBE WHAT THESE AWARDS MIGHT LOOK LIKE. SO AS I MENTIONED, THE CANDIDATES HERE WOULD BE IN VIVO GENETIC THERAPIES FOR RARE GENETIC DISEASES. THE APPLICANT WOULD HAVE TO HAVE HAD OR REQUESTED AN FDA INTERACT MEETING FOR THEIR PLATFORM-BASED APPROACH BECAUSE THAT EARLY FDA INTERACTION IS CRITICAL FOR THESE VERY NOVEL, HIGH-RISK PROJECTS.

THE AWARD WOULD SUPPORT ALL OF THEIR PRECLINICAL ACTIVITIES TO GET TO A MASTER PROTOCOL IND FOR AT LEAST THREE CANDIDATES. AND LIKE THE VALIDATION AWARD, THESE AWARDS WOULD ALSO NOT HAVE A SPECIFIC AWARD CAP, AND THEY WOULD NOT REQUIRE A MINIMUM CO-FUNDING REQUIREMENT FOR THE SAME REASONS THAT I MENTIONED PREVIOUSLY. AND LIKE THE VALIDATION AWARDS AND THE PDEV PROGRAM, THE APPLICANTS FOR THE INNOVATION AWARDS WOULD BE LIMITED TO CALIFORNIA ORGANIZATIONS.

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TO SUPPORT THESE TYPES OF PROJECTS, CIRM REQUESTS FROM THE BOARD TO AUTHORIZE A DEFINED BUDGET OF A $100 MILLION FOR TWO ANNUAL FUNDING CYCLES. AND BECAUSE OF THE DYNAMIC NATURE OF THESE PROJECTS, CIRM WILL ALSO REQUEST A SUPPLEMENT BUDGET THAT WILL ALLOW US TO FURTHER ACCELERATE FUNDED PROJECTS SUBJECT TO A CIRM REQUEST AND APPROVAL PROCESS. SO THE TABLE BELOW DESCRIBES HOW THE $100 MILLION WOULD BE DEPLOYED.

SO IN FISCAL YEAR 26/27, CIRM WOULD REQUEST FROM THE BOARD TO AUTHORIZE $55 MILLION IN FUNDING FOR THE RAPID PROGRAM. $50 MILLION OF THIS ALLOCATION WOULD BE USED TO FUND TWO TO THREE AWARDS. AND $5 MILLION OF THIS WOULD BE RESERVED AS A SUPPLEMENT TO BE DEPLOYED OVER THE LIFETIME OF THE PROGRAM. THE SUPPLEMENT DETAILS ARE DESCRIBED IN THE MEMO AND IN THE CONCEPT. I'M HAPPY TO ELABORATE ON THOSE DURING THE Q AND A IF NEEDED.

IN FISCAL YEAR 27/28 WE ANTICIPATE ASKING THE BOARD TO AUTHORIZE AN ADDITIONAL $45 MILLION, ALL OF WHICH WILL BE DEDICATED TOWARD NEW AWARDS, AND WE ANTICIPATE FUNDING TWO TO THREE AWARDS IN THAT CYCLE.

GIVEN THE DYNAMIC NATURE OF THESE PROJECTS, IT'S ANTICIPATED THAT FUNDS MAY BE

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RECOVERED AS A CONSEQUENCE OF NORMAL AWARD MANAGEMENT OPERATIONS. AND IF ENOUGH FUNDS ARE RECOVERED FROM RAPID AWARDS, CIRM MAY REQUEST TO THE BOARD TO AUTHORIZE ADDITIONAL FUNDING TO OPEN UP A NEW ROUND OR REPLENISH THE SUPPLEMENT BUDGET. THIS WOULD BE AS PART OF A RESEARCH BUDGET APPROVAL PROCESS ON AN ANNUALIZED BASIS.

I'M GOING TO SPEND THE NEXT COUPLE OF SLIDES TALKING ABOUT THE APPLICATION AND REVIEW PROCESS AS WELL AS SOME OF THE AWARD MANAGEMENT FUNCTIONS OF THIS PROGRAM. THEY'RE VERY SIMILAR TO OUR EXISTING PROGRAM, SO I'M NOT GOING TO ELABORATE TOO MUCH ON THESE POINTS.

SO FIRST OF ALL, GIVEN THE UNIQUE NATURE OF THIS PROGRAM, WE WILL REQUIRE CONSULTATIONS PRIOR TO SUBMISSION FROM ALL PROSPECTIVE APPLICANTS. THIS IS MEANT TO HELP ENSURE THE APPLICANTS ARE MEETING THE PLATFORM SCOPE AND READINESS ELIGIBILITY REQUIREMENTS AND TO ALSO GIVE THAT ASSURANCE TO THE APPLICANT BEFORE THEY EMBARK ON WHAT ARE MOST DEFINITELY GOING TO BE LENGTHY PROPOSALS.

THE RAPID PROGRAM WILL UTILIZE EXISTING APPLICATION AND GWG REVIEW PROCESSES. SO ALL APPLICANTS WILL BE REQUIRED TO SUBMIT THE COMPLETE APPLICATION AT THE TIME OF DEADLINE. AND IF

NECESSARY, IF WE HAVE A LARGE AMOUNT OF APPLICATIONS THAT NEED TO BE REDUCED IN ORDER TO GO TO SCIENTIFIC REVIEW, THE GRANTS WORKING GROUP WILL CONDUCT A POSITIVE SELECTION PROCESS SIMILAR TO WHAT WE'VE DONE IN THE PAST FOR OTHER PROGRAMS.

AND LASTLY, LIKE ALL OF OUR CURRENT PROGRAMS, THE GRANTS WORKING GROUP WILL SCORE THESE SUBMISSIONS ON A NUMERICAL 1 TO 100 SCORING SYSTEM TO AID THE ARS IN MAKING FUNDING DECISIONS.

ON THE AWARD MANAGEMENT SIDE, WE WILL UTILIZE EXISTING AWARD MANAGEMENT MECHANISMS TO ENSURE THAT RAPID PROJECTS ADHERE TO THE PROGRAM OBJECTIVE AND EXPECTED OUTCOMES. SO GIVEN THE DYNAMIC NATURE OF THESE PROJECTS AGAIN, WE ANTICIPATE UPPING OUR PROACTIVE AWARD MANAGEMENT PRACTICES, HAVING MORE INTERACTION WITH THE AWARDEE, BEING THERE WHEN THEY HAVE THOSE FDA INTERACTIONS TO ENSURE THAT WE'RE IN LOCKSTEP WITH THE PROJECT TEAM ON THE EXECUTION OF THESE PROJECTS.

AND LIKE ALL OF OUR PDEV AND CLIN2 PROGRAMS, THE RAPID AWARDS WILL BE DRIVEN BY PERFORMANCE DRIVEN OPERATIONAL MILESTONE STRUCTURE. SO ALL THE FUNDS WILL BE DISBURSED UPON SUCCESSFULLY MEETING THE OM CRITERIA ON A TIMELY MANNER. WE WILL ALSO USE THE OM'S HERE IN THIS PARTICULAR INSTANCE

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TO ENSURE THAT THESE PROJECTS ARE DELIVERING ON THE PLATFORM EFFICIENCIES AND ALSO DRIVING TOWARD THE EXPECTED OUTCOME OF CLINICAL VALIDATION FOR MULTIPLE CANDIDATES.

ANY OM DELAYS WILL TRIGGER EVALUATION AND POTENTIAL ACTION WHICH IS SIMILAR TO OUR EXISTING PROGRAMS. AND THE NOTICE OF AWARD WILL DEFINE SUSPENSION EVENTS THAT COULD HALT FUNDING UNTIL THOSE EVENTS ARE RESOLVED AS ALSO A STANDARD FEATURE OF OUR EXISTING AWARD MECHANISMS. SO WE'LL LEVERAGE ALL OF THESE TOOLS TO ENSURE THAT OUR INVESTMENT IN THESE PROJECTS IS PROTECTED AND THAT WE ARE EFFECTIVELY DRIVING THEM TOWARD THE EXPECTED OUTCOME.

LASTLY, I WANT TO STRESS A MAJOR COMPONENT OF THE SUCCESS OF THIS PROGRAM WILL BE BASED ON TIMELY KNOWLEDGE AND DATA SHARING. SO WE VIEW THIS AS TWO PARALLEL MECHANISMS. FIRSTLY, WE EXPECT AND WILL REQUIRE ALL RAPID AWARDEES TO SHARE IN REAL TIME THEIR STUDY DESIGNS, THEIR DATA, THEIR RESOURCES, AND THEIR REGULATORY EXPERIENCE AMONG CIRM AWARDEES. THIS IS INTENDED TO CAPTURE AND LEVERAGE THE BROAD AMOUNT OF EXPERTISE WITHIN THE CIRM AWARDEE NETWORK TO HELP NOT ONLY THESE PROJECTS, BUT ALSO OUR PDEV AND CLIN2 PROJECTS

LEARNED FROM THE SAME EXPERIENCES.

AT THE SAME TIME, WITHIN THE AWARD LIFE CYCLE, WE WILL REQUIRE THESE PROJECTS TO SHARE THEIR RELEVANT DATA, THEIR STUDY DESIGNS, AND THEIR FDA INTERACTIONS WITH THE PUBLIC TO ENSURE THAT THESE PROJECTS ARE ESTABLISHING AND ADVANCING BEST PRACTICES FOR PLATFORM-BASED THERAPY DEVELOPMENT GIVEN THE GREAT DYNAMIC NATURE OF DEVELOPMENT RIGHT NOW FOR GENETIC THERAPIES.

GIVEN THE NATURE OF THIS PROGRAM, WE WOULD LIKE TO HAVE EARLY OUTREACH TO APPLICANTS. SO IF THE BOARD WERE TO APPROVE THIS CONCEPT THIS MONTH, WE WILL EMBARK ON AN OUTREACH STRATEGY THAT IS INTENDED TO PROMOTE RAPID, IS INTENDED TO FACILITATE DISCUSSIONS ABOUT PLATFORM-BASED APPROACHES, AND TO FACILITATE COLLABORATIONS AND RESOURCE SHARING SO THAT APPLICANTS CAN PUT THE BEST PROPOSALS FORWARD WHEN THE SUBMISSION DEADLINE COMES AROUND FOR THE RAPID PROGRAM.

THIS OUTREACH MAY INCLUDE EARLY INTERACTIONS WITH PROSPECTIVE APPLICANTS, ENGAGING WITH EXPERTS AND PATIENT ADVOCACY ORGANIZATIONS, AND HOLDING FORUMS AND WORKSHOPS THAT CONVENE KEY STAKEHOLDERS.

SO IF THE BOARD WERE TO APPROVE THIS

CONCEPT IN JANUARY, WE WILL WORK TOWARD A MID-YEAR APPLICATION DEADLINE. AND WE'RE PROJECTING A NINE-MONTH TIMELINE FROM APPLICATION OVER TO AWARD START, WHICH WOULD PUT THE RAPID AWARDS, THE FIRST WAVE OF THOSE, ON TRACK TO START IN THE EARLY PART OF 2027.

SO WITH THAT, IF YOU'VE BEEN KEEPING COUNT, I'VE PROBABLY SAID RAPID, MULTIPLE, AND DYNAMIC ABOUT A HUNDRED TIMES. AND I WOULD LIKE, ON BEHALF OF CIRM, TO REQUEST THAT THE SCIENCE SUBCOMMITTEE ENDORSE THE PROPOSED RAPID PROGRAM CONCEPT FOR ICOC APPROVAL WITH AN INITIAL ALLOCATION OF $100 MILLION IN THE FIRST TWO FUNDING CYCLES. THANK YOU.

CHAIRMAN FISCHER-COLBRIE: GREAT, SHYAM. EXCELLENT PRESENTATION.

I JUST WANT TO MAKE A FEW COMMENTS. FIRST OF ALL, THIS RAPID APPROACH IS REALLY A DIRECT OUTGROWTH OF THE GENERAL EVOLUTION OF THE FDA REGULATORY PROCESSES THAT HAVE BEEN HEADED TOWARDS MAKING IMPROVEMENTS IN PARTICULAR IN THE RARE DISEASE CATEGORY WHICH ARE HIGHLY PROBLEMATIC FROM THE TRADITIONAL REGULATORY APPROACHES. AND AS YOU POINTED OUT, THAT WAS ACCELERATED SIGNIFICANTLY WITH THE BABY KJ EXPERIENCE AND THE DRIVE BY PATIENT

GROUPS TO EFFECT CHANGE.

AND SO WHAT THIS IS IS ALMOST A REAL-TIME RESPONSE FROM CIRM TO LEVERAGE THE CHANGES IN THE REGULATORY ENVIRONMENT. AND IT'S A REFLECTION OF THE TEAM'S CLOSENESS WITH THE FDA AND WITH THE REGULATORY PROCESSES HISTORICALLY TO BE ABLE TO COME UP WITH A NEW APPROACH AND A NEW PLATFORM FOR ACCELERATION.

AND IT'S IMPORTANT TO NOTE THOSE ARE ALL KEY CHARACTERISTICS OF MEETING THE CIRM STRATEGIC ALLOCATION FRAMEWORK. AND THAT IS, TO WIT, IN THREE AREAS. ONE IS ACCELERATION OF CURES. THE SECOND IS THE MECHANISMS AND GOALS WITH RESPECT TO THE STRATEGIC ALLOCATION FRAMEWORK AROUND RARE DISEASE SOLUTIONS. AND THE THIRD IS FUNCTIONALLY TO CONTINUE TO BUILD PLATFORM CAPABILITIES THAT HAVE THE OPPORTUNITY FOR REPLICATION AND THEN IN TURN POTENTIALLY DRIVE COSTS DOWN AND EXPAND OTHER ORGANIZATIONS TO GET INTO THESE CRITICAL AREAS.

SO I'M VERY IMPRESSED WITH WHAT THE PROPOSAL IS HERE. AND WITH THAT, I'M ASKING FOR AN APPROVAL PROCESS HERE. SO DO WE HAVE A PROPOSAL APPROVAL AND SECOND FOR THIS APPLICATION?

VICE CHAIR BONNEVILLE: SO MOVED.

DR. MELTZER: SECOND.

CHAIRMAN FISCHER-COLBRIE: SECOND. GREAT. WHO WAS THE SECOND, JUST TO CONFIRM?

DR. MELTZER: CAROLYN.

CHAIRMAN FISCHER-COLBRIE: CAROLYN. GREAT. SO WITH THAT, LET'S OPEN UP FOR DISCUSSION AND QUESTIONS BY PEOPLE ON THE CALL. AND WE'LL GET TO SEE IF THERE'S ANY PUBLIC COMMENT AFTER THAT, BUT ANY QUESTIONS OR COMMENTS FROM THE SCIENCE SUBCOMMITTEE? IS THAT SHAWNA?

DR. STARK: YES, THAT'S RIGHT. SHAUNA STARK. THANK YOU.

I THINK THIS IS A FABULOUS IDEA, A REALLY INNOVATIVE MODEL. I THINK WE'VE SEEN MORE PLATFORM TRIALS SHOWING UP. I THINK THIS IS GREAT.

I THINK MY QUESTION IS GOING TO COME DOWN TO THE MONEY. HOW DOES -- WE DON'T HAVE A NUMBER OF GRANTS ALLOCATED. MY UNDERSTANDING IS THE BUDGET'S NOT REALLY SET PER PROJECT. SO HOW DOES IT IMPACT THE OVERALL BUDGET ALLOCATION ACROSS THE PROGRAMS?

DR. PATEL: IT'S A GREAT QUESTION.

CHAIRMAN FISCHER-COLBRIE: GO AHEAD.

DR. PATEL: YES, IT'S A GREAT QUESTION. SO WHAT WOULD HAPPEN HERE IS THAT IN THE PA IT WOULD SPECIFY THAT FOR THIS FIRST YEAR THERE'S A $50 MILLION ALLOCATION AND WE EXPECT TO FUND TWO TO

THREE AWARDS. AND SO THAT WOULD SET THE EFFECTIVE CAP. SO THE AWARD -- APPLICATIONS WOULD PROPOSE THEIR BUDGETS. WE DO A BUDGET REVIEW; BUT WHEN THE APPLICATION REVIEW SUBCOMMITTEE APPROVES THAT AWARD, THAT WOULD EFFECTIVELY BE THE MAXIMUM AWARD AMOUNT FOR THAT PROJECT. AND WE WOULD CONTINUE TO DO ANOTHER BUDGET REVIEW AFTER THAT DURING CONTRACTING, AND WE MONITOR THOSE BUDGETS OVER TIME.

SO EFFECTIVELY WHAT THAT MEANS IS THAT WHEN IT COMES TO THE BOARD FOR APPROVAL, THESE PROPOSALS COME TO THE BOARD FOR APPROVAL, THERE WILL HAVE TO BE DECISIONS MADE ON WHICH ONES CAN BE FUNDED UP TO THE $50 MILLION AWARD AMOUNT, TOTAL AWARD AMOUNT. I'M ANTICIPATING BEING ABLE TO FUND TWO TO THREE WITH THAT SORT OF AN ALLOCATION. BUT IT REALLY DEPENDS ON THE QUALITY OF THE PROJECTS, THE SCALE OF THOSE PROJECTS, AND WHAT THE BOARD WANTS TO FUND. SO IT COULD BE ONE, IT COULD BE TWO, IT COULD BE THREE, OR IT COULD BE EVEN MORE.

DR. STARK: THANK YOU.

CHAIRMAN FISCHER-COLBRIE: PAT.

DR. LEVITT: HI, SHYAM. A FEW QUESTIONS. I'LL START WITH THE DOLLAR AMOUNT. WHAT WAS THE EVALUATION YOU DID TO COME UP WITH THAT NUMBER? AND THESE AWARDS, I CAN'T REMEMBER, WHAT'S THE DURATION

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THAT YOU ANTICIPATE FOR THESE AWARDS, FOR A SINGLE AWARD? HOW MANY YEARS?

DR. PATEL: YEAH. SO I'LL ADDRESS THE SECOND QUESTION FIRST. SO FOR THE VALIDATION, IT'S SIX YEARS. AND THAT'S BASED ON OUR CURRENT TIMELINE FOR WHAT IT TAKES TO GO FROM A PRE-IND MEETING TO COMPLETION OF A CLINICAL TRIAL WITHIN OUR EXISTING PDEV AND CLIN2. WE ANTICIPATE THAT THE BULK OF THAT WOULD BE THE CLINICAL TRIAL ACTIVITY.

FOR THE INNOVATION AWARD, WHICH IS THE PRECLINICAL SIDE, THOSE WOULD BE 3.5 YEARS BECAUSE WE'RE EXPECTING THEM TO MOVE A LOT FASTER IN THAT RANGE.

IN TERMS OF HOW WE CAME ABOUT WITH THE PROGRAM BUDGET, SO WE RAN SOME SIMULATIONS ON TAKING JUST OUR EXISTING AWARD CAPS FOR PDEV AND CLIN2 AND APPLYING SOME MULTIPLICATION FACTORS TO THOSE AND WHERE WE WOULD END UP. AND ALSO LOOKING AT -- IT WAS DIFFICULT TO GAUGE, BUT GETTING A SENSE OF HOW MUCH FUNDING HAD GONE INTO, FOR EXAMPLE, THE CHOP TEAM'S SOMATIC CELL AND GENE EDITING CONSORTIUM EFFORTS. AND SO REALLY WITHIN THAT RANGE, WE'RE LOOKING AT PROJECTS THAT MIGHT BE BETWEEN 20 TO $30 MILLION FOR THAT VALIDATION AND LOWER FOR THE INNOVATION.

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SO WHAT WE WANTED TO DO WAS ENSURE THAT WE CAN FUND AT LEAST THREE TO FIVE PROJECTS AND HAVE A BUDGET TO BE ABLE TO DO THAT AND TO ALSO EXPEND THAT BUDGET OVER TWO YEARS TO REALLY CAPTURE THE INNOVATION IN THIS DYNAMIC FIELD.

DR. LEVITT: BECAUSE THE CHOP TEAM JUST GOT A NEW NIH AWARD, RIGHT, FOR AFTER THE SUCCESS. IT'S 14 MILLION FOR FOUR YEARS. THAT'S TOTAL COSTS. AND, OF COURSE, OUR INDIRECTS THAT WE PAY ARE MUCH LESS. SO OUR DIRECT COSTS THAT ARE BEING PROPOSED ARE OBVIOUSLY MUCH LARGER THAN WHAT -- AND I'M NOT SUGGESTING NIH THESE DAYS IS A FABULOUS STANDARD TO GO BY. I HAVE LOTS OF QUESTIONS ABOUT THE CURRENT MAKEUP OF THE FDA AND HOW WE'RE INVOLVED THERE BECAUSE I DON'T REALLY QUITE UNDERSTAND THE EXPERTISE THAT THEY HAVE TO ADDRESS THE VARIOUS PLATFORM PROPOSALS. BUT THAT'S -- I'LL LEAVE THAT UP TO YOU AND YOUR TEAM TO DECIDE.

I GUESS THE OTHER QUESTION I HAVE IS BABY KJ NEONATE LIVER METABOLIC DISORDER, AND I KNOW THAT PEOPLE ARE LOOKING AT THAT AND SAYING IT'S GOING TO APPLY TO ALL RARE DISEASES. WHAT ARE YOUR THOUGHTS THERE BECAUSE THEY SPENT A LOT OF YEARS STUDYING UREA CYCLE AND OTHER METABOLIC DISORDERS THAT ARE SINGLE GENE DISORDERS AND HAVE A HUGE AMOUNT OF

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BIOLOGICAL UNDERSTANDING OF THE INDEPENDENCE OF SOME OF THESE PATHWAYS IN TERMS OF THEIR CAPABILITY OF BEING CORRECTED THROUGH GENE EDITING. SO WHAT'S YOUR THOUGHT ABOUT THE DOMAINS IN WHICH THIS IS GOING TO BE MORE PROBABLY GREATER APPLICATION THAN IN OTHERS? I'M SURE YOU THOUGHT ABOUT THIS.

DR. PATEL: YEAH. SO I THINK IN TERMS OF GENE EDITING, AND I'LL ALSO ASK MY COLLEAGUES TO WEIGH IN ON THEIR EXPERIENCE BECAUSE THEY HAVE BEEN DOING A DEEPER DIVE. SO WITH RESPECT TO GENE EDITING, YOU'RE RIGHT, THAT IF WE'RE LOOKING AT NONVIRAL APPROACHES COMING IN, THEY'RE PROBABLY GOING TO BE TARGETING THE LIVER WHERE THERE IS THE GREATEST AMOUNT OF DATA RIGHT NOW AND UNDERSTANDING THOSE DISEASES.

IF YOU BROADEN OUT TO, LET'S SAY, SOME BIO APPROACHES, FOR EXAMPLE, AAV, THERE'S A LOT OF UNDERSTANDING OF SOME OF THE NEURODEVELOPMENTAL DISEASES WHERE THE AAV CAN DELIVER THAT VECTOR AND THAT PAYLOAD TO THE CELLS. AND IN THOSE INSTANCES, IN OUR OWN PORTFOLIO AND IN SOME OTHER AREAS OUTSIDE OF OUR PORTFOLIO, THERE HAVE BEEN SOME PLATFORM EFFICIENCIES REALIZED FOR THAT SORT OF A MECHANISM WHERE, BECAUSE THE DELIVERY VEHICLE IS THE SAME, YOU CAN REDUCE A SIGNIFICANT AMOUNT OF ANIMAL TESTING.

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BUT IT WOULD HAVE TO BE A PROPOSAL THAT DEMONSTRATES HOW YOU CAN TAKE A VIRAL VECTOR THAT'S CNS TARGETED AND REALLY DEMONSTRATE PLATFORM EFFICIENCIES ACROSS THAT.

JIM AND LISA, IF YOU WANT TO ADD ANY OTHER PROJECTS THAT YOU'VE BEEN LOOKING AT.

DR. CAMPANELLI: THE INBORN ERRORS OF METABOLISM TARGETING THE LIVER ARE OBVIOUS. AND RIGHT NOW IT'S JUST A POSSIBILITY. SO WE WOULD BE CONTRIBUTING TO THE ACTUAL INNOVATION OF WHAT THE FDA IS TALKING ABOUT IN ORDER -- ERRORS OF IMMUNITY WOULD BE A NEXT STEP VERY MUCH LIKE THE INBORN ERRORS OF METABOLISM POTENTIALLY. AND THEN THINKING BROADER, CYSTIC FIBROSIS IS AN AREA THAT MIGHT BE AMENABLE TO ONE OF THESE APPROACHES, WHICH YOU MIGHT NOT HAVE THOUGHT OF.

DR. LEVITT: RIGHT. AND TO THE CURRENT PLATFORM, THE CURRENT PLATFORMS, I ASSUME, INCLUDE COMPONENTS THAT REALLY ADDRESS ISSUES OF, FOR EXAMPLE, OFF TARGET OR IMMUNOLOGICAL OR THE POTENTIAL FOR NEGATIVE IMMUNOLOGICAL RESPONSIVENESS, RIGHT, BECAUSE THOSE ARE TWO AREAS THAT ARE THE RISK FACTORS, RIGHT. SO I ASSUME THE PLATFORMS WOULD BY DEFINITION NEED TO INCLUDE WAYS IN WHICH THOSE ARE IDENTIFIED AS LOW OR NO RISK, RIGHT?

DR. PATEL: YEAH. AND SO, FOR EXAMPLE, WITH RESPECT TO THE UREA CYCLE DISORDER CANDIDATES, THE BULK OF THE TESTING ON THE OTHER CANDIDATES IS FOCUSED ON PRETRIAL TARGET TESTING TO DEMONSTRATE THE SAFETY PROFILE THERE. SO IT WOULD HAVE TO BE A RISK-BASED STRATEGY ON WHICH TESTING IS APPLIED TO THE BASKET OF THOSE THERAPIES AND WHAT'S BEING RESERVED FOR THE MAIN CANDIDATE.

DR. LEVITT: IS THE PROGRAM FLEXIBLE ENOUGH SO THAT IF YOU GET MORE APPLICATIONS THAN YOU ANTICIPATED? THERE'S GOING TO BE SOME NUMBER OF CURRENT CALIFORNIA RESEARCH GROUPS THAT ARE SET UP TO BE ABLE TO DO THIS AND TAKE ADVANTAGE OF THIS PROGRAM. IT'S NOT GOING TO BE BROADLY APPLIED, RIGHT? YOU HAVE TO ALREADY BE PRETTY EXPERT IN THIS AREA. IS THERE ENOUGH FLEXIBILITY FROM YOUR PERSPECTIVE TO MODIFY WHAT YOU ARE GOING TO PROVIDE PER GRANT IF YOU GET EXCITING, REALLY INNOVATIVE PROPOSALS, AND IT'S MAYBE MORE THAN TWO OR THREE, TO BE ABLE INCREASE THE POSSIBILITY OF DISCOVERY THAT WOULD MAKE A BIG DIFFERENCE? BECAUSE PUTTING ALL OUR EGGS INTO TWO OR THREE GROUPS, I'M SURE THEY'LL ALL BE GREAT, BUT YOU NEVER KNOW.

SO I'M ASKING ABOUT FLEXIBILITY. IN THE SLIDE DECK IT SAYS TWO TO THREE, BUT YOU MENTION

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COULD BE UP TO FIVE. SO THAT INDICATED TO ME THAT YOU'RE THINKING MORE FLEXIBLY, RIGHT, OR NOT?

DR. PATEL: YEAH. SO I THINK OVERALL, IF WE WERE TO PROJECT OUT THE WHOLE $100 MILLION, WE COULD ANTICIPATE FIVE OR SIX PROJECTS IN TOTAL, RIGHT. BUT THAT'S BASED ON US LOOKING AT OUR CURRENT AWARD CAPS AND PERFECTING ON THAT. IF THERE'S SIGNIFICANT EFFICIENCIES REALIZED AND THE NUMBER OF CANDIDATES ARE NOT HUGE, IT'S POSSIBLE THAT THEY MIGHT EVEN HAVE SMALLER BUDGETS AND WE DON'T KNOW.

IN ORDER TO, I THINK, ENABLE WHAT YOU ARE ASKING, BECAUSE THERE'S ALWAYS GOING TO BE THAT CONSTRAINT OF $50 MILLION FOR THAT PROGRAM FOR THAT FISCAL YEAR, THAT WOULD LIMIT HOW MANY WE CAN FUND. BUT I THINK ONE OF THE THINGS THAT WE ARE GOING TO ENCOURAGE IN THE PA AND IN OUR DISCUSSIONS WITH THE APPLICANTS IS TO LEVERAGE ANY RESOURCE SHARING, ANY IN-KIND SUPPORT, ANY VOLUNTARY CO-FUNDING THAT THEY CAN GET. AND WE'VE SEEN NOT ONLY IN OUR PROGRAMS, BUT ALSO IN OUR COLLABORATIONS WITH FNIH ON THE AGCT, THAT THERE ARE MANY VENDORS AND SERVICE PROVIDERS THAT FIND WAYS TO DO RISK AND COST SHARING FOR INNOVATIVE APPROACHES. AND SO IT'S POSSIBLE THAT ALL THOSE COULD FACTOR IN TO REDUCE THE BUDGET

FOR ANY INDIVIDUAL PROJECT.

VICE CHAIR BONNEVILLE: AND, PAT, I THINK SOMETHING TO CONSIDER IS IN THE NEXT ALLOCATION, IF THE BOARD FEELS THAT MORE MONEY NEEDS TO BE ALLOCATED TO THIS PROGRAM, THERE IS THE OPPORTUNITY IN THE BUDGET CYCLE TO DO SO IF THAT'S THE RECOMMENDATION FROM THE TEAM.

DR. LEVITT: OKAY. THANK YOU.

CHAIRMAN FISCHER-COLBRIE: ARE THERE OTHER QUESTIONS? I'M NOT ABLE TO SEE ALL THE HANDS. SO I DON'T KNOW IF THERE'S OTHER QUESTIONS OR COMMENTS.

MR. TOCHER: IT DOESN'T APPEAR SO AT THE MOMENT.

CHAIRMAN FISCHER-COLBRIE: OKAY. ANY QUESTIONS OR COMMENTS FROM THE PUBLIC?

MR. TOCHER: IT DOESN'T APPEAR SO, MARK.

CHAIRMAN FISCHER-COLBRIE: OKAY. SCOTT, WITH THAT, IF YOU CALL THE ROLL ON THE VOTE.

MR. TOCHER: SURE. MARIA BONNEVILLE.

VICE CHAIR BONNEVILLE: YES.

MR. TOCHER: DEBORAH DEAS.

DR. DEAS: YES.

MR. TOCHER: MARK FISCHER-COLBRIE.

CHAIRMAN FISCHER-COLBRIE: YES.

MR. TOCHER: ELENA FLOWERS.

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DR. FLOWERS: YES.
MR. TOCHER: JUDY GASSON.
DR. GASSON: YES.
MR. TOCHER: VITO IMBASCIANI.
CHAIRMAN IMBASCIANI: YES.
MR. TOCHER: PAT LEVITT.
DR. LEVITT: YES.
MR. TOCHER: SHLOMO MELMED.
DR. MELMED: YES.
MR. TOCHER: CAROLYN MELTZER. CHRIS MIASKOWSKI.
DR. MIASKOWSKI: YES.
MR. TOCHER: SHAUNA STARK.
DR. STARK: YES.
MR. TOCHER: KAROL WATSON.
DR. WATSON: YES.
MR. TOCHER: KEITH YAMAMOTO. GREAT. THANK YOU. AND THE MOTION CARRIES.
CHAIRMAN FISCHER-COLBRIE: GREAT. THANK YOU. WITH THAT, LET'S PROCEED TO THE NEXT ITEM ON THE AGENDA. AND DR. ROSA CANET-AVILES IS GOING TO PRESENT ON THE PREFERENCES.
DR. CANET-AVILES: MR. FISCHER-COLBRIE, THE CHAIRS OF THE SCIENCE SUBCOMMITTEE AND THE NEURO TASK FORCE, DR. PAT LEVITT AS WELL AND DR. CAROLYN

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MELTZER, AS WELL AS THE MEMBERS OF THE SCIENCE SUBCOMMITTEE, AND THE PUBLIC.

SO THE PRESENTATION THAT I'M GOING TO SHOW TODAY, JUST AS AN UPDATE, HAS A FEW -- A LITTLE ADDITIONAL CONTENT, AND WE WILL REPOST THE MATERIAL FOR THE ICOC ONCE WE HAVE THE DISCUSSION. THESE REFINEMENTS HAVE BEEN MADE IN RESPONSE TO SOME BOARD MEMBER QUESTIONS AFTER WE POSTED LAST WEEK.

SO I WOULD LIKE TO START BY TAKING A STEP BACK AND EXPLAINING WHY WE ARE BRINGING THIS CONVERSATION TO THE SUBCOMMITTEE TODAY. OVER THE LAST YEAR AS WE LAUNCHED THE NEW PROGRAM CONCEPTS AND THE PROGRAM ANNOUNCEMENTS, WE INTRODUCED PREFERENCES AS PART OF A BROADER EFFORT TO HELP CIRM TRANSLATE PUBLIC INVESTMENT INTO MEANINGFUL PATIENT IMPACT WITHIN THE FINITE TIME FRAME THAT WE HAVE.

AND SINCE THEN WE HAVE NOW COMPLETED IN SOME CASES UP TO TWO FUNDING CYCLES. FOR PDEV AND CLIN2 WE'VE ALREADY DONE TWO CYCLES OF PRESUBMISSIONS. THUS FAR WE'VE DONE ONE. AND THIS GAVE US AN OPPORTUNITY TO PAUSE AND LOOK AT HOW THIS APPROACH IS WORKING IN PRACTICE.

THE PURPOSE OF TODAY'S DISCUSSION AND PRESENTATION IS TO MAKE SURE THAT WE ARE ALL ANCHORED IN THE SAME UNDERSTANDING OF WHAT THE

PREFERENCES WERE INTENDED TO DO, HOW THEY HAVE BEEN APPLIED ALONGSIDE SCIENTIFIC REVIEW, AND WHAT ARE THE EARLY SIGNALS THAT WE ARE STARTING TO SEE. SOMETIMES THE DATA IS STILL TOO LIMITED TO DRAW CONCLUSIONS, BUT WE ARE GOING TO PRESENT WHAT WE HAVE. AND ONE THEME THAT HAS COME UP REPEATEDLY IN CONVERSATIONS IS THE IMPORTANCE OF KEEPING PREFERENCES FROM BECOMING TOO RESTRICTIVE.

SO THE INTENT OF THE PREFERENCES, JUST TO CLARIFY, IS TO GUIDE PRIORITIZATION, NOT TO NARROW THE SCIENCE OR TO EXCLUDE NOVEL IDEAS -- AND WE CAN GO INTO THIS -- OR TO REPLACE PEER REVIEW. ALL OF OUR PROGRAMS ARE STILL OPEN, AND SCIENTIFIC QUALITY AND READINESS CONTINUE TO BE FOUNDATIONAL.

SO TODAY'S PRESENTATION IS REALLY A FRAMING AND LEARNING DISCUSSION. WE WILL WALK THROUGH THESE EARLY SIGNALS, SHARE WHAT WE THINK WE ARE SEEING, AND THEN HEAR FROM YOU ABOUT WHAT ADDITIONAL PORTFOLIO LEVEL ANALYSIS COULD BE MOST HELPFUL BEFORE WE COME BACK IN MARCH FOR A DEEPER CONVERSATION ABOUT REFINEMENT FOR OUR FISCAL YEAR 26/27. NEXT SLIDE. AND THANK YOU, LIZ, FOR PASSING THE SLIDES.

SO TODAY'S PRESENTATION, AS I WAS SAYING, IS A CHECKPOINT, AN OPPORTUNITY TO ALIGN ON

UNDERSTANDING, BRING UP QUESTIONS, AND MAKE SURE WE ARE ASKING FOR THE ANALYSIS THAT WILL BEST SUPPORT THOUGHTFUL DECISIONS BY THIS SUBCOMMITTEE AND THE BOARD LATER ON IN MARCH.

SO THIS SLIDE IS MEANT TO GROUND THE REST OF THE DISCUSSION IN THE OPERATING REALITY THAT WE ARE WORKING WITHIN. PROP 14 SIGNIFICANTLY EXPANDED OUR MANDATE BOTH IN TERMS OF SCIENTIFIC CONDITION AND EXPECTATIONS AROUND PATIENT IMPACT. IN PARTICULAR, IT REINFORCED PRIORITIES AROUND THE CENTRAL NERVOUS SYSTEM AND MADE ACCESS AND AFFORDABILITY AN EXPLICIT PART OF OUR RESPONSIBILITY, NOT JUST SOMETHING TO CONSIDER DOWNSTREAM.

AT THE SAME TIME, OUR FUNDING REMAINS FINITE AND TIME BOUND. WE HAVE DEFINED REMAINING -- WE HAVE A DEFINED REMAINING RUNWAY, AND THE VOLUME OF SCIENTIFIC STRONG APPLICATIONS WE'VE RECEIVED CONSISTENTLY EXCEEDS WHAT WE CAN SUPPORT. THIS IS NOT A REFLECTION OF A DECLINE IN QUALITY. IT IS A REFLECTION OF DEMAND OUTPACING CAPACITY, AND IT IS NOT UNIQUE TO CIRM. IT HAPPENS IN ALL FUNDING AGENCIES.

SO TAKEN TOGETHER, THESE TWO REALITIES CREATE THE CENTRAL TENSION THAT WE ARE TRYING TO

MANAGE, WHICH IS EXPANDED EXPECTATIONS FOR IMPACT WITHIN FIXED RESOURCES AND A FINITE TIME FRAME. THE GOAL, THEREFORE, IS NOT SIMPLY TO FUND EXCELLENT SCIENCE, BUT TO TRANSLATE PUBLIC INVESTMENT INTO THERAPIES THAT CAN REALISTICALLY REACH PATIENTS WITHIN OUR LIFETIME, INCLUDING CONSIDERATION OF FEASIBILITY, READINESS, AND DOWNSTREAM ACCESS.

THE BOARD APPROVED A STRATEGIC FRAMEWORK AND IMPACT GOALS AS THE ROADMAP TO ACHIEVE THAT BACK IN SEPTEMBER OF 2024. SO PREFERENCES ARE THE MECHANISM THAT WE'VE INTRODUCED TO HELP NAVIGATE THIS CHALLENGE. NOT A SUBSTITUTE OF SCIENTIFIC REVIEW, BUT IS A WAY TO FOCUS LIMITED RESOURCES TOWARDS THE HIGHEST LIKELIHOOD OF MEANINGFUL PATIENT THERAPY.

SO THE REST OF THE PRESENTATION IS GOING TO BUILD FROM THIS REALITY. HOW WE ATTEMPTED TO OPERATIONALIZE PRIORITIZATION, WHAT ARE THE EARLY SIGNALS THAT WE ARE SEEING, AND WHERE FURTHER ANALYSIS IS NEEDED BEFORE CONSIDERING ANY REFINEMENT. AND THEN IN MARCH WE CAN CONSIDER THE REFINEMENTS.

SO STARTING FROM THAT REALITY, WHICH IS THIS EXPANDED MANDATE, FINITE RESOURCES, AND A LIMITED RUNWAY, THE PRACTICAL QUESTION HERE BECOMES

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HOW DO WE MOVE FROM MANY STRONG APPLICATIONS TO A PORTFOLIO THAT HAS THE HIGHEST LIKELIHOOD OF DELIVERING REAL PATIENT IMPACT WITHIN CIRM'S LIFETIME. AND WE ARE GOING TO DEFINE ALL OF THIS. NEXT SLIDE.

THIS SLIDE SHOWS THE ROLE THAT PREFERENCES ARE INTENDED TO PLAY, NOT AS A SUBSTITUTE OF SCIENTIFIC REVIEW, BUT AS A WAY TO FOCUS LIMITED RESOURCES TOWARDS APPLICATIONS MOST ALIGNED WITH THE IMPACT GOALS THAT WE DEFINED. ON THE LEFT WE START WITH A LARGE POOL OF APPLICATIONS. MANY OF THESE ARE SCIENTIFICALLY STRONG, BUT THEY DRIVE IN TERMS OF READINESS, FEASIBILITY, ALIGNMENT WITH THE STATUTORY MANDATES, AND THE LIKELIHOOD OF TRANSLATING INTO THERAPIES WITHIN THE TIME FRAME THAT WE HAVE.

THE STARS REPRESENT APPLICATIONS THAT MOST ALIGN WITH OUR GUIDING PRINCIPLES INCLUDING, CLINICAL IMPACT, FEASIBILITY, ACCESS AND AFFORDABILITY CONSIDERATIONS, AND RELEVANCE TO OUR MANDATES. IMPORTANTLY, THE ABSENCE OF A STAR DOESN'T MEAN THAT THERE IS NO SCIENTIFIC MERIT OR THAT THE PROPOSAL IS NOT STRONG. IT ONLY REFLECTS THAT IT HAS LESS ALIGNMENT WITH THESE SPECIFIC IMPACT-ORIENTED CRITERIA.

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PREFERENCES HELP ENRICH THE POOL BY BRINGING FORWARD APPLICATIONS THAT ARE MORE LIKELY TO CONTRIBUTE TO NEAR AND MIDTERM IMPACT GIVEN OUR CONSTRAINTS. THAT ENRICHED POOL THEN MOVES INTO SCIENTIFIC AND TECHNICAL REVIEW WHERE THE MERIT, THE RIGOR, AND THE READINESS ARE EVALUATED IN DEPTH. THE KEY POINT IS THAT PREFERENCES SHAPE WHICH APPLICATIONS RISE FOR REVIEW WHILE THE PEER REVIEW DETERMINES WHICH OF THOSE ARE ULTIMATELY FUNDED. THIS ALLOWS CIRM TO BOTH UPHOLD THE SCIENTIFIC EXCELLENCE AND MAKE DELIBERATE CHOICES ABOUT HOW PUBLIC FUNDS ARE DEPLOYED TO ACHIEVE OUR GOALS.

I WANT TO PAUSE HERE, THIS IS IMPORTANT, AND ACKNOWLEDGE WHAT WE'VE BEEN HEARING BECAUSE THIS FEEDBACK IS AN IMPORTANT PART OF WHY WE ARE HAVING TODAY'S DISCUSSION. SOME OF THE CONCERNS REFLECT UNCERTAINTY ABOUT HOW PREFERENCES, PRESUBMISSION, QUALIFICATION INTERACTS WITH SCIENTIFIC REVIEW AND WHETHER THE PROPOSALS THAT DID NOT ADVANCE WERE FULLY CONSIDERED ON SCIENTIFIC GROUNDS.

OTHER CONCERNS REFLECT QUESTIONS ABOUT WHETHER PREFERENCES MIGHT UNINTENTIONALLY FAVOR CERTAIN MODALITIES OR PATHWAYS OR WHETHER PROGRESSION WITHIN THE CIRM PORTFOLIO IS BEING APPROPRIATELY RECOGNIZED.

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WE'VE ALSO HEARD A DESIRE FOR GREATER CLARITY AROUND HOW QUALIFICATION SCORING, PREFERENCES, AND INTENT FIT TOGETHER AND WHAT PREFERENCES ARE DESIGNED TO DO VERSUS WHAT THEY ARE NOT DESIGNED TO DO. MORE IMPORTANTLY, A LOT OF THIS FEEDBACK IS LESS ABOUT DISAGREEMENT WITH THE GOALS AND MORE ABOUT UNDERSTANDING THE LOGIC; IN OTHER WORDS, HOW THE PIECES FIT TOGETHER, HOW DECISIONS ARE SEQUENCED, AND HOW THIS ULTIMATELY CONNECTS TO DELIVERING THERAPIES FOR PATIENTS.

THAT FEEDBACK HAS HELPED US, AND IT HAS HELPED US RECOGNIZE THAT WE NEED TO BE MORE CLEAR AND MORE EXPLICIT IN HOW WE COMMUNICATE THE RATIONALE BEHIND THESE CHOICES AND ALSO IN HOW WE SHOW THE LINK BETWEEN PRIORITIZATION DECISIONS AND IMPACT AND ALSO ABOUT THE FACT THAT, IF WE WANT TO MAKE AN IMPACT WITH THE CONSTRAINTS THAT WE HAVE OF FUNDING AND TIME, WE NEED TO MAKE SOME HARD CHOICES.

TAKING THAT ALL THAT TOGETHER, THIS CONTEXT THAT WE ARE OPERATING WITHIN, THE ROLE OF THE PREFERENCES, AND THE FEEDBACK, THIS BRINGS US TO WHAT WE ARE TRYING TO ACCOMPLISH IN TODAY'S DISCUSSION, WHICH IS IN THE NEXT SLIDE.

SO THE PURPOSE OF TODAY IS NOT TO DEBATE INDIVIDUAL OUTCOMES OR TO MAKE DECISIONS ABOUT

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PENDING PREFERENCES. IT'S FOCUSED ON THESE THREE OBJECTIVES. FIRST, WE WANT TO WALK BACK THROUGH THE RATIONALE FOR THE PREFERENCES, HOW THEY CONNECTED TO PROPOSITION 14, TO THE STRATEGIC ALLOCATION FRAMEWORK, AND TO THE PRACTICAL CONSTRAINTS WE ARE WORKING WITHIN.

SECOND, WE WANT TO SHARE WHAT WE HAVE BEEN LEARNING FROM THE FIRST ROUND OF CYCLES OF PRE-PREFERENCE APPLICATIONS, THE PRESUBMISSIONS, FOR PDEV AND CLIN2 AND DISC4. AND THOSE ARE EARLY SIGNALS. THEY'RE NOT CONCLUSIONS, BUT THEY HELP US UNDERSTAND WHETHER THE APPROACH IS FUNCTIONING IN THE WAY THAT IT WAS INTENDED.

AND THIRD, WE WANT TO USE THIS COMMITTEE'S PERSPECTIVE TO IDENTIFY WHAT PORTFOLIO LEVEL ANALYSES ARE NEEDED BEFORE WE COME BACK IN MARCH TO HAVE A MORE SUBSTANTIVE DISCUSSION ABOUT REFINEMENT.

JUST TO CLARIFY, THE LAST SLIDE SHOWS SOME OF THE PORTFOLIO ANALYSIS ALREADY THAT HAVE BEEN SUGGESTED BY BOARD MEMBERS THROUGH PRE-CALLS, AND WE WILL DISCUSS THOSE, AND THEN THE BOARD CAN DECIDE WHETHER THEY WANT TO ADD MORE.

SO FRAMING TODAY THIS WAY ALLOWS US TO STAY FOCUSED ON LEARNING AND ALIGNMENT NOW SO THAT ANY FUTURE DECISIONS ARE GROUNDED IN SHARED

UNDERSTANDING AND DATA. NEXT SLIDE.

WITH THAT FRAMING, BEFORE WE GET INTO ANY SPECIFIC PREFERENCES OR SCORING MECHANICS, IT'S IMPORTANT TO STEP BACK AND MAKE EXPLICIT THE PRINCIPLES THAT GUIDED HOW PREFERENCES WERE DEVELOPED IN THE FIRST PLACE. THESE PRINCIPLES ARE NOT THEORETICAL. THEY ARE THE BACKBONE OF HOW WE DESIGNED THE PRECLINICAL AND THE CLINICAL AND THE PROGRAMS AS WELL AS THE BROADER PORTFOLIO UNDER THE STRATEGIC ALLOCATION FRAMEWORK. THEY REFLECT THE REALITIES THAT WE'VE LEARNED OVER YEARS OF FUNDING THAT EITHER DID OR DIDN'T TRANSLATE INTO THERAPIES THAT REACHED PATIENTS.

SO THE FIRST ONE IS OFFERING POTENTIAL FOR TRANSFORMATIVE CLINICAL IMPACT. WHAT DO WE MEAN BY THAT? WHEN WE TALK ABOUT CLINICAL IMPACT, WE ARE NOT USING IT AS A SYNONYM FOR SCIENTIFIC NOVELTY OR DISEASE IMPORTANCE. IN THE CONTEXT OF PRECLINICAL DEVELOPMENT AND CLIN2, CLINICAL IMPACT MEANS THAT THERE IS A REALISTIC POTENTIAL FOR A THERAPY TO MEANINGFULLY CHANGE OUTCOMES FOR PATIENTS; THAT IS, IN TERMS OF EFFICACY, DURABILITY, SAFETY, OR BURDEN OF CARE COMPARED TO WHAT EXISTS OR POTENTIALLY IS COMING IN THAT POOL OF APPLICATIONS OR PRESUBMISSIONS.

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THIS PRINCIPLE FORCES US TO ASK NOT WHETHER THE SCIENCE IS INTERESTING, BUT IF THIS WORKS, DOES IT ACTUALLY MATTER FOR PATIENTS. THIS IS JUST ONE PRINCIPLE. WE WILL GET TO OTHERS THAT DO TAKE INTO ACCOUNT THE SCIENCE.

THE SECOND ONE IS THAT IT ADDRESSES BOTTLENECKS TO ACCESS, AFFORDABILITY, AND TRANSLATIONAL FEASIBILITY. THIS PRINCIPLE REFLECTS ONE OF THE MOST IMPORTANT LESSONS EMBEDDED IN THE SAF, WHICH ARE THAT EARLY DECISIONS AFFECT DOWNSTREAM ACCESS. AND WE'VE BEEN WORKING ON THIS UNDER THE UMBRELLA OF THE ACCESSIBILITY AND AFFORDABILITY WORKING GROUP AND ITS LEADERSHIP.

IN BOTH PDEV AND CLIN2, WE HAVE SEEN THAT CHOICES AROUND MODALITY, DELIVERY, MANUFACTURING STRATEGY, AND CLINICAL IMPLEMENTATION CAN MAKE THE DIFFERENCE BETWEEN A THERAPY THAT'S TECHNICALLY SUCCESSFUL AND ONE THAT IS ACTUALLY USABLE AT SCALE. SO THIS PRINCIPLE IS NOT ABOUT PRICING POLICY OR REIMBURSEMENT MANDATES. IT'S ABOUT WHETHER THE PROPOSED APPROACH ACKNOWLEDGES AND BEGINS TO ADDRESS NON-BOTTLENECKS, FOR EXAMPLE, OVERLY COMPLEX MANUFACTURING OR UNREALISTIC DELIVERY ASSUMPTIONS. PREFERENCES TIED TO SCALABLE MODALITIES AND FEASIBLE DELIVERY PATHS ARE DIRECT EXPRESSIONS OF THIS

PRINCIPLE.

THE THIRD ONE IS THAT IT FILLS CRITICAL FUNDING GAPS AND ADVANCES CIRM'S STATUTORY MANDATES. CIRM'S ROLE IS NOT TO FUND EVERYTHING. IT'S TO FUND WHAT OTHERS CANNOT OR WILL NOT, IN PART. AND THIS PRINCIPLE REFLECTS THE REALITY THAT CERTAIN DISEASE AREAS AND MODALITIES OR STAGES OF DEVELOPMENT ARE PERSISTENTLY UNDERFUNDED BY FEDERAL AGENCIES OR THE PRIVATE SECTOR DESPITE THEIR POTENTIAL IMPORTANCE. IN PDEV, FOR EXAMPLE, THIS SHOWS UP HOW WE THINK ABOUT ENABLING TRANSLATIONAL WORK THAT COULD OTHERWISE STALL. IN CLIN2 IT SHOWS UP SUPPORTING TRIALS THAT CARRY SCIENTIFIC OPERATIONAL RISK, BUT ALIGN STRONGLY WITH OUR MISSION. AND THIS PRINCIPLE ALSO EXPLICITLY INCORPORATES PROP 14 MANDATES, INCLUDING THE CNS AND THE PLURIPOTENT STEM CELL-BASED APPROACHES AS PART OF OUR PRIORITIZATION LOGIC.

THE FOURTH PRINCIPLE IS CAN REALISTICALLY ACHIEVE KEY REGULATORY AND DEVELOPMENT PATH WITHIN CIRM'S FINITE RUNWAY? THIS PRINCIPLE IS ONE OF THE HARDEST AND ALSO ONE OF THE MOST IMPORTANT. IT DOESN'T MEAN THAT AMBITIOUS SCIENCE IS DISCOURAGED. IT MEANS THAT WE HAVE TO BE HONEST ABOUT TIMELINES, DEPENDENCIES, AND WHAT FUNDING -- CIRM FUNDING CAN

REASONABLY ENABLE WITHIN THE YEARS THAT WE HAVE LEFT.

IN CLIN2 THIS IS WHERE READINESS, REGULATORY CLARITY, AND OPERATIONAL FEASIBILITY MATTERS SO MUCH. IN PDEV THIS IS WHY THE FOCUS ON WHETHER A PROGRAM IS POSITIONED TO MAKE A MEANINGFUL REFLECTION SUCH AS ENABLING AN IND RATHER THAN ACCUMULATING MORE EXPLORATORY DATA IS COUNTED AS. THIS PRINCIPLE PROTECTS US BOTH, CIRM AND THE APPLICANTS, FROM INVESTING HEAVILY IN PROGRAMS THAT, EVEN IF SCIENTIFICALLY SOUND, ARE UNLIKELY TO REACH MEANINGFUL MILESTONES WITHIN OUR LIFETIME.

THE FIFTH PRINCIPLE IS THAT IT ADDRESSES DISEASES AFFECTING CALIFORNIANS. AS A PUBLIC FUNDING AGENCY OF CALIFORNIA, CIRM HAS A RESPONSIBILITY TO ENSURE THAT OUR PORTFOLIO REFLECTS DISEASES AND CONDITIONS THAT MEANINGFULLY AFFECT CALIFORNIANS. THIS DOESN'T MEAN FUNDING ONLY COMMON DISEASES, NOR DOES IT EXCLUDE RARE DISEASES. WHAT IT MEANS IS IT REQUIRES US TO BE THOUGHTFUL ABOUT THE OVERALL BALANCE OF THE PORTFOLIO AND THE POPULATIONS ULTIMATELY SERVED. AND IT REINFORCES THE PUBLIC ACCOUNTABILITY DIMENSION OF THE STRATEGY THAT WE HAVE AND HELPS ENSURE THAT OUR INVESTMENT STRATEGY REMAINS ALIGNED WITH THE VOTERS' INTENT.

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AND LASTLY, WE HAVE THE PRINCIPLE OF DIVERSIFYING CIRM'S ACTIVE AWARD PORTFOLIO. THIS FINAL PRINCIPLE IS ACTUALLY VERY IMPORTANT GIVEN THE CONCERNS THAT HAVE BEEN RAISED ABOUT PREFERENCES BECOMING RESTRICTIVE. DIVERSIFICATION IS A GUARDRAIL. IT EXISTS TO PREVENT OVERCONCENTRATION IN A SINGLE DISEASE AREA OR MODALITY OR DEVELOPMENT PATHWAY EVEN IF THAT AREA IS POPULAR OR WELL REPRESENTED AMONG APPLICATIONS. IN PRACTICAL TERMS, THIS PRINCIPLE IS WHY THE NOVELTY UNDERREPRESENTED DISEASE AREAS RELATIVE TO THE ACTIVE PORTFOLIO ARE EXPLICITLY CONSIDERED IN PDEV AND CLIN2 SCORING AT DIFFERENT STAGES. IT IS ALSO WHY PREFERENCES ARE NOT BINARY GATES. THIS PRINCIPLE ENSURES THAT GENUINELY NOVEL OR NON-OBVIOUS APPROACHES, INCLUDING OUTLIERS, HAVE A PATHWAY FORWARD RATHER THAN BEING COUNTED OUT BY PROGRAMS THAT SIMPLY ALIGN WITH THE MOST COMMON PREFERENCES. AND AS I SAID, THEY ARE CONSIDERED AT DIFFERENT STAGES IN THE PRESUBMISSION OR QUALIFICATION PROCESS.

WITH THOSE GUIDING PRINCIPLES IN MIND, I AM GOING TO NOW SHOW HOW THEY WERE TRANSLATED INTO A PRACTICAL, PROGRAM-SPECIFIC PREFERENCE RUBRIC. AND THIS IS ACTUALLY WHERE WE HAVE PROVIDED MORE DETAIL. AND IN THE NEXT SLIDES I'M GOING TO WALK THROUGH THE

PDEV AND THE CLIN2 RUBRICS. IN BOTH CASES THE KEY THING TO KEEP IN MIND IS THAT THESE ARE ALIGNMENT AND QUALIFICATION TOOLS, AND THEY ARE NOT SUBSTITUTES FOR SCIENTIFIC REVIEW.

ARE WE ALL OKAY? GOOD.

SO THE PDEV PROGRAM IS INTENDED TO ENRICH CIRM'S CLINICAL PIPELINE. COMPARED TO THE EXISTING PORTFOLIO, IT SHOULD ADVANCE STATE-OF-THE-ART THERAPEUTIC TECHNOLOGIES THAT ADDRESS A BROAD RANGE OF DISEASES AFFECTING CALIFORNIANS.

THE FIRST LINE THAT WE HAVE IN THE PRESUBMISSION RUBRIC FOR PDEV REFLECTS ALIGNMENT WITH CORE AREAS WHERE CIRM HAS A CLEAR ROLE AND RESPONSIBILITY EITHER BECAUSE OF STATUTE OR BECAUSE OF DOWNSTREAM ACCESS AND FEASIBILITY CONSIDERATIONS. APPLICANTS RECEIVE UP TO THREE POINTS IF THEIR PROJECT ALIGNS WITH AT LEAST ONE OF THESE AREAS: PLURIPOTENT STEM CELL-DERIVED THERAPIES, DISEASES OF THE CENTRAL NERVOUS SYSTEM, OR IN VIVO GENE THERAPIES. IMPORTANTLY, THIS IS NOT ADDITIVE. MEETING ONE CRITERION IS ENOUGH TO GET THE THREE POINTS. AND THIS WAS DESIGNED DELIBERATELY TO AVOID STACKING MODALITY BIAS OR FORCING PROJECTS TO FIT MULTIPLE BOXES.

THE NEXT SET OF PREFERENCES CAPTURES

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READINESS AND TRANSLATIONAL MOMENTUM. THIS INCLUDES NONVIRAL NUCLEIC ACID DELIVERY, EVIDENCE OF EARLY FDA ENGAGEMENT THROUGH A PRE-IND OR INTERACT MEETING, AS WELL AS PROGRESSION FROM EARLIER CIRM PROGRAMS, SUCH AS DISC2 OR TRAN1. THE SIGNALS HELP US UNDERSTAND WHERE A PROJECT SITS ON THE DEVELOPMENT PATH AND WHETHER CIRM FUNDING IS LIKELY TO BE CATALYTIC AT THIS STAGE. AGAIN, THESE ARE PREFERENCES AND NOT REQUIREMENTS.

THE NEXT ONE IS UNDERREPRESENTED DISEASE AREAS. THIS CATEGORY IS ABOUT PORTFOLIO BALANCE, AS I WAS MENTIONING, AND IT GOES WITH THE DIVERSITY GUIDING PRINCIPLE. WE EXPLICITLY LOOK AT HOW REPRESENTED DISEASE AREA ALREADY IS WITHIN CIRM'S ACTIVE AWARDS AND GIVES MODEST ADDITIONAL WEIGHT TO AREAS THAT ARE UNDERREPRESENTED. THE INTENT HERE IS DIVERSIFICATION, NOT PRIORITIZATION OF RARITY OR EXCLUSION OF WELL-REPRESENTED DISEASES.

VICE CHAIR BONNEVILLE: ROSA, THAT POINT SYSTEM IS VARIABLE, ZERO TO TWO. CAN YOU EXPLAIN THAT A LITTLE MORE?

DR. CANET-AVILES: YES. WE CAN EXPLAIN THAT A LITTLE MORE. BASICALLY YOU HAVE -- THE ZERO TO TWO POINTS, YOU GET ZERO IF THE DISEASE AREA IS MORE THAN 10 PERCENT. ONE IS THE DISEASE AREA IS

BETWEEN 5 PERCENT AND LESS THAN 10 PERCENT. AND TWO POINTS IS THE DISEASE AREA IS 5 PERCENT OR LESS. AGAIN, ONE OF THE THINGS I WAS GOING TO MENTION IS THAT SOME OF THESE SCORING METHODS HAVE, THIS IN PARTICULAR, HAD A SLIGHT MODIFICATION BETWEEN THE FIRST AND THE SECOND ROUND THAT I CAN ASK SHYAM TO SPEAK ABOUT A LITTLE BIT MORE IF YOU WANT. GOOD?

VICE CHAIR BONNEVILLE: THAT'S FINE.

DR. CANET-AVILES: THANK YOU. WHERE WERE WE?

VICE CHAIR BONNEVILLE: NOVELTY.

DR. CANET-AVILES: NOVELTY CRITERIA. THANK YOU. THE NOVELTY CRITERIA EXISTS SPECIFICALLY TO PREVENT PREFERENCES FROM BECOMING EXCLUSIONARY AND TO ENSURE THAT STRONG OUTLIER IDEAS STILL HAVE A WAY TO MOVE FORWARD EVEN WHEN THEY DON'T SCORE POINTS ON MULTIPLE PREFERENCES.

NEXT ONE IS THE CLIN2 QUALIFICATION RUBRIC. THIS SLIDE SUMMARIZES THE CLIN2 QUALIFICATION RUBRIC WHICH IS USED AS AN INTERNAL SCREENING TOOL BY THE REVIEW TEAM TO DETERMINE WHICH APPLICATIONS MOVE FORWARD TO ARS REVIEW. IT IS NOT A SCIENTIFIC SCORING RUBRIC, AND IT DOES NOT REPLACE PEER REVIEW. EACH ITEM HERE REFLECTS A DISCRETE PREFERENCE DESIGNED TO ASSESS ALIGNMENT WITH THE

GUIDING PRINCIPLES I MENTIONED A COUPLE SLIDES AGO.

THE FIRST SET OF PREFERENCES INCLUDES PLURIPOTENT STEM CELL-DERIVED THERAPIES AND DISEASES OF THE CNS. EVERYTHING IS ALIGNED ALSO WITH PDEV WHICH ARE EXPLICIT PROP 14 PRIORITIES. IN VIVO GENE THERAPY IS INCLUDED HERE INDIRECTLY, RESPONDING TO STATUTORY MANDATE BECAUSE OF ITS POTENTIAL FOR SCALABLE DELIVERY AND BROADER PATIENT ACCESS. SO THE STATUTORY MANDATE COULD LINK TO ACCESSIBILITY.

NONVIRAL GENETIC THERAPIES ARE INCLUDED TO RECOGNIZE EMERGING APPROACHES THAT MAY REDUCE SAFETY OR MANUFACTURING CONSTRAINTS. WE ALSO ACCOUNT WITHIN THE CLIN2 QUALIFICATION RUBRIC FOR ACCELERATED REGULATORY DESIGNATION SUCH AS RMAT OR BREAKTHROUGH OR FAST TRACK BECAUSE MATERIALLY THEY CHANGE THE DEVELOPMENT TIMELINES AND SIGNAL REGULATORY ALIGNMENT. PROGRESSION FROM EARLIER CIRM AWARDS IS ALSO REFLECTING STEWARDSHIP OF PRIOR INVESTMENTS. AND CALIFORNIA-BASED ORGANIZATIONS REFLECT THE TAXPAYER-FUNDED NATURE OF THE PROGRAM. FINALLY, PIVOTAL TRIALS RECEIVE ADDITIONAL WEIGHT BECAUSE THEY REPRESENT THE FASTEST AND MOST DIRECT PATH TO POTENTIAL LICENSURE AND PATIENT IMPACT.

VICE CHAIR BONNEVILLE: ROSA, CAN YOU GO BACK TO THE PDEV QUALIFICATIONS REALLY QUICKLY?

SO THE TARGET -- THE UNDERREPRESENTED IN CIRM ACTIVE PORTFOLIO THAT HAS A ZERO TO TWO, IS THAT NOT SOMETHING -- YOU SAID THAT ALL THE PDEV AND CLIN HAD THE SAME QUALIFICATIONS. THEY WERE JUST USED DIFFERENTLY. SO HERE IT IS, FOR THE PRESUBMISSION, THE LAST TWO, THE TARGETING DISEASE AREA AND THEN THE NOVELTY. SO WHERE DOES THAT COME INTO PLAY IN THE CLIN BECAUSE PART OF, I THINK, CONVERSATION HAS BEEN AROUND THE PREFERENCES WERE, I THINK WHAT THE BOARD -- THE DISCUSSION THE BOARD HAD WAS, LIKE YOU MENTIONED, WE DIDN'T WANT PREFERENCES TO BE LIMITING. AND SO I GUESS -- THOSE TWO WOULD SEEM TO HELP WITH THAT REQUEST. I DON'T SEE THEM LISTED IN THE CLIN, AND I DON'T KNOW THAT I NOTICED THAT BEFORE.

DR. CANET-AVILES: YEAH. GREAT QUESTION. SHOWS THAT YOU ARE PAYING A LITTLE ATTENTION.

VICE CHAIR BONNEVILLE: I DON'T KNOW ABOUT THAT.

DR. CANET-AVILES: YOU ARE LISTENING TO ME. YEAH. NO, THAT'S A VERY GOOD QUESTION, MARIA.

AND THE TWO CRITERIA THAT YOU ARE SPEAKING TO, WHICH ARE VERY IMPORTANT, AND THEY ALIGN VERY STRONGLY WITH THE SIXTH GUIDING PRINCIPLE WHERE IN THE QUALIFICATION RUBRIC OF THE POSTED CLIN2 PROGRAM

ANNOUNCEMENT THEY GET TRANSLATED INTO THE QUALIFICATION SCORING PROCESS WHICH INCLUDES TIEBREAKING CRITERIA THAT WE HAVEN'T TALKED ABOUT. AND THE REVIEW TEAM DOES THIS. AND I'M GOING TO DEFER TO MY COLLEAGUE, DR. SAMBRANO, TO EXPLAIN HOW THIS WAS TRANSLATED.

VICE CHAIR BONNEVILLE: I'M JUST CURIOUS WHY HERE, WHY IS IT DONE AS A TIEBREAKER HERE, BUT IT'S USED DIFFERENTLY IN PDEV IF THAT'S WHAT WAS IN THE PROGRAM ANNOUNCEMENT OR THE CONCEPT PLAN -- SORRY -- WHEN IT WAS DISCUSSED OR WAS IT NOT? I THOUGHT THAT'S WHAT WE WERE GETTING TO.

DR. SAMBRANO: OKAY. WELL, I'LL EXPLAIN HOW IT IS THAT IT'S DONE. I THINK PART OF IT IS THAT THESE WERE DEVELOPED SEPARATELY WITH THE DIFFERENT TEAMS. SO PDEV VERSUS CLIN. THE WAY CLIN WORKS IS THAT IT WAS FOLLOWING UP ON THE ESTABLISHED QUALIFICATION PROCESS THAT WE HAD IN PLACE ALREADY. AND SO THE CRITERIA AND HOW THAT WORKS IS WE START WITH OBJECTIVE CRITERIA THAT WE NEED TO ASSESS. AND SO THAT STEP IS DONE AND THE PREFERENCES ARE SUCH AS LISTED HERE THAT CAN BE ASCERTAINED VERY CLEARLY ONE WAY OR THE OTHER AND DONE QUICKLY. THAT WILL LEAD YOU TO A HIERARCHY OF THESE PROJECTS THAT THEN WE TIE-BREAK.

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AND SO THE FIRST STEP IN TIEBREAKING IS TO BRING IT TO THE GRANTS WORKING GROUP. AND SO THEY ASSESS THE VALUE PROPOSITION. AND SO WITH THAT VALUE PROPOSITION, THEY'RE LOOKING AT THREE QUESTIONS. THEY'RE LOOKING AT THE POTENTIAL TO PROVIDE MEANINGFUL AND SUBSTANTIAL IMPROVEMENT IN CLINICAL OUTCOMES, EXPECTED IMPACT OF ADDRESSING THE UNMET MEDICAL NEED ON PATIENTS, CAREGIVERS, HEALTHCARE SYSTEM. AND THEN THIRD, THE FEASIBILITY AND PRACTICALITY OF THE THERAPY UPTAKE BY PATIENTS, HEALTHCARE PROVIDERS, AND PAYERS. AND SO THEY SCORE AGAINST THAT IN ORDER TO BREAK TIES.

AND WHERE WE INSERTED THE NOVELTY, AT LEAST IN THE CURRENT PROCESS, IS SHOULD THERE STILL BE A TIE, THEN THE CLINICAL TEAM WOULD USE THAT IN ORDER TO DISTINGUISH BETWEEN APPLICATIONS THAT WOULD ADVANCE OR WOULD NOT.

BUT IN TERMS OF THINKING ABOUT PREFERENCES, I THINK ONE OF THE THINGS IS THESE ARE NOT MEANT, AND I THINK WE'VE SAID IT BEFORE, TO BE STATIC. OUR EXPECTATION IS THAT OVER TIME THESE ARE GOING TO CHANGE. AND DEPENDING ON WHAT WE GET, WE WANT TO CHANGE THEM SO THAT WE CAN --

VICE CHAIR BONNEVILLE: EVOLVE.

DR. SAMBRANO: YES, EVOLVE, TWEAK THEM,

AND SO ON. SO I THINK EVEN THOUGH NOVELTY WE KIND OF PUSH TO THE BACK, AND PART OF THE REASON WAS THAT WE THOUGHT IT TO BE MORE SUBJECTIVE THAN THE OTHERS THAT WE HAD AND HARDER TO ASSESS AS SUCH, BUT I THINK THERE ARE WAYS IN WHICH YOU CAN MAKE NOVELTY MORE OBJECTIVE, WHICH IS KIND OF ALIGNED WITH WHAT PDEV IS DOING IN TERMS OF YOU DEFINE A SPECIFIC PORTFOLIO LIKE OUR CLIN PORTFOLIO. IT'S EITHER IN THERE OR IT'S NOT. IF IT'S NOT, THEN WE GIVE THE POINT. IF IT IS, WE DON'T OR HOWEVER. SO YOU CAN MAKE IT OBJECTIVE IF WE CHOOSE TO DO THAT GOING FORWARD, BUT, AGAIN, WITH THE EXPECTATION THAT WE WILL EVOLVE IT.

VICE CHAIR BONNEVILLE: THANK YOU.

DR. CANET-AVILES: THANK YOU, GIL. AND ONE WAY OF EVOLVING THIS, AND THIS CAN BE PART OF THE DISCUSSION IN MARCH, EVEN TODAY INCLUDING TO MARCH IS THAT WE COULD ADD THE NOVELTY CRITERIA AS PART OF ONE OF THE MAIN QUALIFICATION CRITERIA AS GIL IS SAYING. AND THAT COULD BE A RECOMMENDATION BASED ALSO ON THIS STRONG MESSAGE THAT WE ARE GETTING FROM SOME PRE-CALLS AND FROM BOARD MEMBERS AFTER WE POSTED THAT THE OUTLIERS GET MISSED. AND WE WANT TO ENSURE THAT STRONG OUTLIER IDEAS STILL HAVE A WAY TO MOVE FORWARD EVEN WHEN THEY DON'T

SCORE POINTS ON MULTIPLE PREFERENCES.

WITH THAT SAID, I WAS NOTIFIED THAT WE HAD MADE A CHANGE, AND THIS IS IMPORTANT. IF YOU CAN GO TO THE PDEV, JUST FOR ANY APPLICANTS THAT ARE LISTENING, IT'S IMPORTANT. YOU SEE THE TARGETING DISEASE AND UNDERREPRESENTED AREA IS ACTUALLY ONE POINT, AND IT'S THE NOVELTY, THE ONE THAT HAS ZERO TO TWO POINTS. JUST WANT TO CLARIFY THIS, AND WE WILL UPDATE THIS FOR THE BOARD MEETING. IT WAS A MISTAKE WE MADE WHEN WE POSTED THIS SLIDE. OKAY?

MS. MANDAC: CHRIS HAD HER HAND RAISED. CHRIS, JUST DOUBLE-CHECKING.

DR. MIASKOWSKI: GIL ANSWERED MY QUESTION. I WAS WONDERING ABOUT THE PROCESS TO DO THIS EVALUATION. SO THANKS.

DR. CANET-AVILES: AND, AGAIN, THIS IS DIFFERENT FOR THE PDEV, THE PRESUBMISSION RUBRIC, BECAUSE THESE ARE PRESUBMISSIONS THAT IS EVALUATED IN A VERY OBJECTIVE WAY BY THE TEAM. THERE IS A WHOLE PROCESS. FOR THE QUALIFICATION IS ACTUALLY THE REVIEW TEAM TOGETHER WITH GRANTS WORKING GROUP FOR THOSE THAT ARE MORE SUBJECTIVE CRITERIA.

WITH THAT, WE'RE GOING INTO SLIDE NO. 16. THANK YOU, LIZ. WITH THAT FRAMEWORK, I KNOW I USE THAT WORD A LOT, WE'LL NOW SHOW RESULTS FROM THE

FIRST TWO CYCLES OF PDEV AND CLIN2 TO ILLUSTRATE HOW THESE PREFERENCES PLAYED OUT IN PRACTICE STARTING WITH CYCLE 1.

JUST A CLARIFICATION, FOR CYCLE 1, WE HAVE AN ARS FOR BOTH PDEV AND CLIN2. FOR CYCLE 2, WE ONLY HAVE THE PRESUBMISSION AND THE QUALIFICATION CRITERIA. THOSE HAVE NOT BEEN -- WELL, WE DON'T HAVE THE RESULTS OF THE MEETING. OKAY.

THIS SLIDE WILL SUMMARIZE HOW THE PREFERENCE FRAMEWORK PLAYED OUT IN THE FIRST PDEV CYCLE. WE RECEIVED 168 PRESUBMISSIONS REFLECTING WHAT I WAS SAYING, A STRONG DEMAND AND STRONG SCIENCE MOST LIKELY. USING THE PRESUBMISSION RUBRIC, WE INVITED 33 APPLICATIONS FORWARD FOR FULL APPLICATION AND REVIEW, WHICH CORRESPONDS ROUGHLY TO THE TOP 20 PERCENT. AND WHAT'S IMPORTANT HERE IS THE SEPARATION SIGNAL. AMONGST THE INVITED GROUP, 97 PERCENT MET THREE TO FOUR OF THE STATED PREFERENCES; WHEREAS, 42 PERCENT OF THE NONINVITED PROPOSALS MET ZERO OR NON-PREFERENCES. THIS TELLS US THAT THE RUBRIC WAS FUNCTIONING AT LEAST AS INTENDED, NOT EXCLUDING AREAS ARBITRARILY, BUT HELPING DISTINGUISH WHICH PROPOSALS WERE MOST ALIGNED WITH THE PRIORITIES THAT THE BOARD HAD SET WHEN APPROVING THE CONCEPTS.

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OF THE 12 ULTIMATELY FUNDED AWARDS, WE SEE SEVERAL CONSISTENT THEMES. THERE WAS A CLEAR INCREASE IN PROPOSALS WITH STRONGER TRANSLATIONAL READINESS, INNOVATION, AND SCALABILITY. AND MORE THAN HALF REPRESENT PROGRESSIONS OF PRIOR CIRM-FUNDED PROGRAMS. AND THE FUNDED SET IS MORE ENRICHED FOR DISEASE AREAS THAT HAD BEEN UNDERREPRESENTED IN OUR ACTIVE PORTFOLIO. TAKEN TOGETHER, THIS CYCLE RESULTS SUGGESTS THAT THE PREFERENCES ARE NOT NARROWING THE SCIENCE, BUT REBALANCING THE PRECLINICAL PORTFOLIO ACROSS MODALITY, DISEASE AREA, AND PROP 14 CNS PRIORITIES IN A WAY THAT IS INTENTIONAL AND ALIGNED WITH WHAT WE WERE SET TO DO BY THE BOARD WHEN THEY APPROVED OUR STRATEGY. NEXT SLIDE.

THIS SLIDE SHOWS THE DATA FROM THE SECOND CYCLE OF PDEV. AN IMPORTANT CAVEAT IS THAT THESE PRESUBMISSION RESULTS -- THESE ARE PRESUBMISSION RESULTS ONLY. WE HAVE NOT YET COMPLETED FULL APPLICATION REVIEW OR GRANTS WORKING GROUP ASSESSMENT. WHAT WE SEE, HOWEVER, IS THAT THE SAME PATTERN FROM CYCLE 1 HOLDS. WE RECEIVED 126 PRESUBMISSIONS AND INVITED 23 TO FULL APPLICATION, WHICH IS ABOUT ROUGHLY 18 PERCENT. IMPORTANTLY, A HUNDRED PERCENT OF INVITED APPLICATIONS MET THREE TO

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FIVE PREFERENCES WHILE ABOUT A THIRD OF UNINVITED APPLICATIONS MET ZERO TO ONE PREFERENCE. SO THE SIGNAL REMAINS WITH THE CLIN.

TWO ADDITIONAL POINTS RESPOND DIRECTLY TO QUESTIONS THAT WE'VE HAD. FIRST, WE INVITED -- THE INVITED POOL SPANS BROAD DISEASE AREAS, INCLUDING MORE CANCER AND IMMUNOLOGY PROGRAMS THAN IN CYCLE 1. AND SECOND, NEARLY 40 PERCENT OF INVITED APPLICATIONS COULD REPRESENT PROGRESSION WITHIN THE CIRM -- EXISTING CIRM PORTFOLIO IF FUNDED, WHICH IS EXACTLY WHAT WE INTENDED, DISCIPLINED ADVANCEMENT, NOT RANDOM EXPANSION. SO WHILE FINAL FUNDING DECISIONS ARE STILL AHEAD, THE TAKEAWAY IS THAT THE PREFERENCE FRAMEWORK CONTINUES TO DO WHAT IT WAS DESIGNED TO DO, WHICH IS IDENTIFY THE STRONGEST, MOST ALIGNED PROGRAMS EARLY WHILE ALLOWING THE PORTFOLIO TO GROW ACROSS DISEASE AREAS WHERE THE SCIENCE IS READY.

NOW WE'RE GOING TO GO INTO THE CLIN2 CYCLE. I DON'T KNOW IF THERE ARE ANY QUESTIONS, IF YOU WANTED ME TO STOP. I'M GOING TO KEEP GOING, BUT FEEL FREE TO STOP ME. OKAY.

I'LL NOW TURN TO CYCLE 1 OF CLIN2. WE RECEIVED 23 TOTAL APPLICATIONS ALL OF WHICH WERE RANKED USING THE PREFERENCE POINTS AS PART OF THE

QUALIFICATION. FROM THOSE, SEVEN ADVANCED TO FULL REVIEW AND FOUR WERE ULTIMATELY FUNDED. A FEW THINGS ARE WORTH HIGHLIGHTING. FIRST, ALL SEVEN APPLICATIONS THAT ADVANCED TO FULL REVIEW MET THREE TO FOUR PREFERENCE POINTS. SO THE FRAMEWORK CLEARLY DISTINGUISHED TOP TIER. ALL SEVEN TARGETED CNS INDICATIONS, WHICH IS CONSISTENT WITH ONE OF PROP 14 PRIORITIES, AND SIX OR SEVEN INVOLVED EITHER PLURIPOTENT STEM CELL-DERIVED THERAPIES OR IN VIVO GENETIC THERAPIES, AND FOUR ALREADY HAD ADVANCE REGULATORY DESIGNATIONS WHICH SPEAKS TO DEVELOPMENT MATURITY.

LOOKING AT THE FUNDED PROGRAMS, ALL FOUR THAT WE FUNDED HAVE PHYSICAL DELIVERY PATHS ALIGNED WITH OUR ACCESS AND AFFORDABILITY STRATEGY AND THREE REPRESENT PROGRESSIONS OF CIRM-FUNDED PROGRAMS. AND THAT TELLS US THAT THE SYSTEM IS REINFORCING BOTH INNOVATION AND DISCIPLINED PORTFOLIO ADVISEMENT. THE KEY TAKEAWAY IS THAT THE SYSTEM WORKED DIRECTIONALLY AS INTENDED. IT ELEVATED PROGRAMS THAT ARE ALIGNED WITH THE STATUTORY PRIORITIES, CLINICAL READINESS, AND DELIVERY FEASIBILITY. THAT SAID, CYCLE 1 ALSO MADE CLEAR THAT THE RELATIVE WEIGHING OF PREFERENCE MATTERS, AND THAT'S WHERE REFINEMENT COULD COME IN TO ENSURE WE ARE NOT

OVERCONCENTRATING SIGNALS AS THE PORTFOLIO GROWS.

THE NEXT SLIDE IS THE SECOND CYCLE OF CLIN2. AND I'M GOING FASTER BECAUSE I JUST REALIZED THE TIME. AND SCOTT IS GOING TO KILL ME. THIS SLIDE SHOWS WHERE WE ARE FOR -- AND CLAUDETTE TOO -- CLIN2 CYCLE, RECOGNIZING THAT THESE ARE INTERIM RESULTS PENDING GRANTS WORKING GROUP REVIEW AND BOARD APPROVAL.

WE RECEIVED 21 APPLICATIONS ALL OF WHICH WERE RANKED USING THE SAME PREFERENCE-BASED FRAMEWORK. FROM THOSE, SEVEN ADVANCED TO FULL REVIEW, AND EVERY ADVANCING APPLICATION SCORED THREE TO FOUR PREFERENCE POINTS, WHICH IS CONSISTENT WITH WHAT WE SAW IN CYCLE 1. IN TERMS OF COMPOSITION, FOUR TARGET CNS, FIVE REPRESENT PROGRESSIONS FROM THE EXISTING CIRM PORTFOLIO, AND FIVE ARE EITHER IN VIVO GENETIC THERAPIES OR PLURIPOTENT STEM CELL-DERIVED THERAPIES, AGAIN, REFLECTING A STRONG ALIGNMENT WITH THE PREFERENCES THAT THE BOARD SET.

FINAL FUNDING RECOMMENDATIONS WILL FOLLOW THE REVIEW OF JANUARY 27 AND THEN COME BACK TO THE BOARD THROUGH THE NORMAL APPROVAL PROCESS.

SO NOW I'M GOING TO SUMMARIZE. WHEN WE LOOK ACROSS PDEV AND CLIN2 -- I'M ALREADY, YEAH. TOGETHER THE OVERALL PATTERN IS CONSISTENT AND

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DIRECTIONALLY ALIGNED WITH WHAT THE BOARD ASKED US TO DO. AWARDS IN BOTH PROGRAMS REFLECT THE INNOVATION, READINESS, ACCESS AND AFFORDABILITY, AND CNS CRITERIA THAT WERE EXPLICITLY LAID OUT IN THE PROGRAM ANNOUNCEMENTS, NOT INFORMALLY, BUT OPERATIONALLY THROUGH THE QUALIFICATION AND RANKING PROCESS.

THE APPLICATIONS THAT ADVANCED WERE LARGELY CIRM PORTFOLIO PROGRESSIONS. AND WE'VE HAD A LOT OF QUESTIONS ABOUT THAT, AND I JUST WANT TO MAKE THAT POINT. BUT IMPORTANTLY, THEY WERE NOT ADVANCING BECAUSE THEY WERE LEGACY PROJECTS. THEY ADVANCED BECAUSE THEY ALSO MET OTHER MULTIPLE STATED PREFERENCES. SO MANY OF THEM HAD SEVERAL PREFERENCES THAT THEY WERE HITTING.

ANOTHER RESULT, THE PORTFOLIO NOW INCLUDES MORE FEASIBLE AND SCALABLE MODALITIES WHICH STRENGTHENS DOWNSTREAM ACCESS AND AFFORDABILITY POTENTIAL WITHOUT SACRIFICING SCIENTIFIC RIGOR. THAT SAID, I WANT TO BE CLEAR ABOUT THE CAVEATS. THESE ARE EARLY SIGNALS, AND IT IS TOO SOON TO ASSESS PORTFOLIO LEVEL IMPACT. WHAT WE CAN SAY AT THIS STAGE IS THAT THE SYSTEM IS BEHAVING DIRECTIONALLY AS WE INTENDED.

NEXT I'M GOING TO GO INTO THE DISC4. THIS

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IS A BRIEF REMINDER OF WHAT THE BOARD APPROVED LAST YEAR FOR DISC4. THE BOARD APPROVED NEUROLOGICAL DISEASE AS A PREFERENCE FOR THE FY 25/26 DISC4 CYCLE. AND THE PROGRAM WAS OPEN TO ALL COMERS. AS A REMINDER, THIS SLIDE SHOWS HOW THAT ALTERNATIVE STRUCTURE IS INTENDED TO WORK OVER TIME. SOME CYCLES ARE DRIVEN BY THE NEURO TASK FORCE IDENTIFIED NEEDS, WHICH WOULD BE THE ONES THAT ARE NTF BASED, RIGHT, AND WE JUST HAD ONE. AND WE HAD THE NEUROPSYCHIATRIC/NEURODEVELOPMENTAL PRIORITIES AND THEN WE HAD THE NEUROLOGICAL FOCUS. ALL THIS REFLECTS BOARD-SET PREFERENCES, AND CRUCIALLY EVERY CYCLE REMAINS OPEN TO ALL COMERS.

THIS STRUCTURE WILL GIVE THE BOARD A REPEATABLE, TRANSPARENT WAY TO SET DIRECTION YEAR OVER YEAR WHILE WE STILL PRESERVE SCIENTIFIC BREADTH AND FLEXIBILITY. SO FOR THIS YEAR, WHEN WE SET THE NEUROLOGICAL, THIS SLIDE SHOWS HOW THE PREFERENCES WERE OPERATIONALIZED IN THE DISC4 25/26 CYCLE CONSISTENT WITH WHAT'S APPROVED IN THE PROGRAM ANNOUNCEMENT.

AND I WILL JUST SAY THAT THE SCORING WAS NOT PUBLISHED FOR ANY OF THESE PROGRAMS, AND THAT IS NOT IDEAL. THE REASON THAT HAPPENS WAS BECAUSE WE MOVED FAST TO HONOR OUR COMMITMENT TO LAUNCH THESE

PROGRAMS QUICKLY. AND THE SCORING WAS FINALIZED DURING IMPLEMENTATION RATHER THAN BEFORE POSTING, WHICH WE SHOULD HAVE PUBLISHED AND WE WILL MOVING FORWARD.

SO WHAT WE ARE TRYING TO DO IS SHOW NOW HOW WE SCORE THESE THINGS SO EVERYBODY IS -- TO HAVE TRANSPARENCY. THE NEUROLOGICAL DISEASE, SO FOR DISC4, THE NEUROLOGICAL DISEASE PREFERENCE CARRIED 36 PERCENT OF THE TOTAL SCORING WEIGHT. THAT WAS INTENTIONAL AND TRANSPARENT BECAUSE IT REFLECTS THE BOARD'S DECISION TO CLEARLY SIGNAL A PRIORITY FOR THIS CYCLE WHILE STILL KEEPING THE PROGRAM OPEN TO ALL APPLICANTS. YOU COULD COME NOT HAVING NEUROLOGICAL AND KEEPING EVERYTHING ELSE AND YOU MIGHT MAKE IT, RIGHT, BUT IT WILL BE HARD. IMPORTANTLY, PREFERENCE ALIGNMENT WAS NOT THE SOLE DRIVER OF RANKING. 64 PERCENT OF THE SCORE CAME FROM SCIENTIFIC SUBSTANCE WHICH WAS REPRESENTED BY RELEVANCE TO HUMAN DISEASE BIOLOGY, CROSS-DISCIPLINARY, AND SYSTEM LEVEL APPROACHES AS WELL AS INNOVATION IN STEM CELL OR GENETIC RESEARCH. IN OTHER WORDS, PROJECTS STILL HAD TO BE STRONG SCIENCE FIRST. THIS STRUCTURE IS DOING WHAT IT WAS DESIGNED TO DO, WHICH IS TRANSLATE BOARD LEVEL PRIORITIES INTO MEASURABLE SIGNAL WITHOUT COLLAPSING

DISC4 INTO A SINGLE DISEASE PROGRAM OR EXCLUDING HIGH QUALITY WORK OUTSIDE THE PREFERENCE AREA.

I'M GOING TO GO INTO THE RESULTS. THIS SLIDE SHOWS HOW THE DISC4 NEURO PREFERENCE PLAYED OUT AT THE PRESUBMISSION STAGE. AND JUST AS A REMINDER, WE HAVE -- THIS HAS NOT BEEN REVIEWED. IT'S COMING IN FEBRUARY, THE REVIEW, FOR THIS PROGRAM.

WE RECEIVED 138 PRESUBMISSIONS AND 86 PERCENT ALIGNED WITH THE NEURO PREFERENCE. THAT TELLS US THAT THE SIGNAL WAS CLEARLY HEARD BY THE COMMUNITY. FROM THAT POOL, 24 APPLICATIONS WERE INVITED TO FULL APPLICATION AND REVIEW. AND IMPORTANTLY, A HUNDRED OF THOSE INVITED MET THE NEURO PREFERENCE, BUT THEY SPAN A BROAD RANGE OF NEUROLOGICAL DISEASES AND REPRESENT A WIDE DIVERSITY OF MECHANISMS AND SCIENTIFIC APPROACHES.

SO WHAT WE ARE SEEING HERE IS NOT CONVERSION ON A SINGLE DISEASE OR MODALITY. IT'S ACTUALLY ENRICHMENT WITHIN A PRIORITY AREA WHILE PRESERVING SCIENTIFIC BREADTH. FUNDING DECISIONS ARE STILL PENDING, AS I MENTIONED, AND IT WILL BE IN FEBRUARY 2026, BUT AT THIS STAGE THE PREFERENCE IS DOING EXACTLY WHAT IT WAS DESIGNED TO DO, WHICH IS TO SHAPE THE POOL WITHOUT NARROWING THE SCIENCE.

AND NOW I'M GOING TO MOVE INTO WHAT WE'VE LEARNED SO FAR. STEPPING BACK, THERE ARE -- THE INITIAL SIGNALS WE ARE SEEING FROM PREFERENCE SETTING ACROSS PDEV AND CLIN2. FIRST, THE APPLICATIONS THAT ADVANCED TO GRANTS WORKING GROUP REVIEW CONSISTENTLY MET MULTIPLE PREFERENCES. THAT TELLS US THAT THE RUBRIC IS DOING REAL TRIAGE. IT'S NOT ADVANCING PROJECTS ON A SINGLE ATTRIBUTE ALONE.

SECOND, IN CLIN2 WE SEE HIGH PROPORTION OF CNS-FUNDED PROJECTS, WHICH IS CONSISTENT WITH THE STATED PREFERENCE AND CONFIRMS THAT, WHEN WE WEIGH A PRIORITY, IT SHOWS UP CLEARLY AT THE OUTCOME LEVEL. IN CONTRAST, PDEV SHOWS A MUCH WIDER SPREAD ACROSS DISEASE AREAS AND MODALITIES, WHICH REFLECTS BOTH THE EARLY STAGE OF THE SCIENCE AND THE WAY PREFERENCES WERE DESIGNED TO GUIDE AND NOT CONSTRAIN THAT PORTFOLIO.

AND FINALLY, ACROSS BOTH PROGRAMS A LARGE FRACTION OF FUNDED PROJECTS ARE CIRM PORTFOLIO PROGRESSIONS, OVER 50 PERCENT IN PDEV AND ROUGHLY 75 PERCENT IN CLIN2, WHICH SUGGESTS THAT THE SYSTEM IS REINFORCING CONTINUITY WHILE STILL APPLYING DIRECTIONAL FILTERS. IMPORTANTLY, THESE ARE EARLY SIGNALS AS, AGAIN, NO FINAL CONCLUSIONS. THE JANUARY PRESENTATION, AS I MENTIONED AT THE

BEGINNING, IS MEANT TO TEE UP THE QUESTIONS FOR THE BOARD. AND IN MARCH WE'LL COME BACK WITH A FULL PORTFOLIO LEVEL ANALYSIS AND ANY PROPOSED REFINEMENTS BASED ON YOUR GUIDANCE.

MR. TOCHER: PAT HAS HIS HAND RAISED.

DR. CANET-AVILES: YES. I WAS JUST GOING TO PUT THE LAST SLIDE, BUT I'M HAPPY TO ANSWER QUESTIONS. I'LL JUST PUT THIS HERE. BASICALLY THIS SLIDE IS PLANNED ANALYSIS, AND PAT LEVITT, DR. LEVITT, ACTUALLY WAS THE ONE THAT BROUGHT THESE SUGGESTIONS. AND OUR QUESTION COULD BE BASED ON ALL WHAT WE SAW TODAY, WHAT OTHER ANALYSIS, IF ANY, WOULD WE LIKE TO SEE IN MARCH. AND WITH THAT, I THANK YOU FOR YOUR ATTENTION, AND I'M SORRY I WAS SO LONG. I DON'T KNOW IF I WAS LONG, BUT TRIED MY BEST. PAT.

DR. LEVITT: I JUST NEED A -- MAYBE TWO CLARIFICATIONS. ONE IS YOU HAD THAT SLIDE UP WHERE WE HAD THE INITIAL DISC WAS FOCUSED ON NEURODEVELOPMENTAL DISORDERS AND PSYCHIATRIC, AND THEN THIS ONE IS FOCUSED ON NEUROLOGICAL. RIGHT? I THINK THAT'S WHAT YOU SAID. AND I'M TRYING TO UNDERSTAND WHERE THIS FOCUS -- YOU SAID A HUNDRED PERCENT ARE NEURO, NEUROLOGICAL, BUT EXCLUDED NEURODEVELOPMENTAL AND PSYCHIATRIC, OR YOU MEANT

NEURO MEANING THE NEURO DEFINED IN PROPOSITION 14, WHICH WAS ANY NERVOUS SYSTEM DISORDER.

DR. CANET-AVILES: THE NEURO DEFINED IN PROPOSITION 14, EVERYTHING. THAT WAS ACTUALLY WHAT YOU, THE BOARD, ASKED US TO HAVE THERE.

DR. LEVITT: RIGHT. I JUST THINK IT'S A LITTLE CONFUSING BECAUSE THERE ARE THINGS THAT ARE NEUROLOGICAL AND NOT, BUT THERE ARE THINGS THAT ARE NEURODEVELOPMENTAL THAT ARE NEUROLOGICAL. AND, OF COURSE, FOR SOME NEUROPSYCHIATRIC, IT'S ALSO NEUROLOGICAL. SO I DON'T KNOW -- TO ME THE TERMINOLOGY IS TO FOLLOW WHAT'S IN PROPOSITION 14 BECAUSE THAT'S THE EMPHASIS AREA AND THAT'S HOW THE SCORING IS BEING DONE. IS IT NEURO BASED ON THE DEFINITION IN PROPOSITION 14?

DR. CANET-AVILES: YEAH. SO YOU HAVE A GREAT POINT, PAT. AND WE WILL CHANGE THAT TO MAKE SURE THAT IT ALIGNS WITH WHAT WE'VE DONE AND WHAT THE BOARD. SO WE WILL SAY NEURO AS DEFINED BY PROP 14 INSTEAD OF NEUROLOGICAL, WHICH IS -- YEAH.

DR. LEVITT: AND THEN JUST THE OTHER CLARIFICATION I HAVE. SO THERE'S A POINT GIVEN IF IT'S NONVIRAL DELIVERY. AND ALTERNATIVE DELIVERIES FOR THE CENTRAL NERVOUS SYSTEM ARE FAR BEHIND OTHER ORGAN SYSTEMS. SO I'M WONDERING HOW THAT -- MAYBE

IT'S TOO LONG A CONVERSATION TO HAVE, BUT I'M WONDERING HOW THAT PLAYED OUT BECAUSE, RIGHT, DELIVERY TO THE CNS, THERE'S BEEN MORE WORK DONE ON VIRAL DELIVERY THAN THERE HAVE BEEN ON ANYTHING ELSE, AND IT'S STILL BEHIND THE EIGHT BALL IN TERMS OF GETTING THESE OTHER -- LIPOSOMES AND OTHER THINGS ARE ACTUALLY TARGETING, NOT JUST INTO THE NERVOUS SYSTEM, BUT TARGETING THE RIGHT CELLS.

SO I'M WONDERING IF THAT ENDS UP BEING A DISADVANTAGE FOR SCORING.

AND THEN THE OTHER THING I'LL MENTION, AND WE DON'T HAVE TO DEAL WITH IT TODAY, MAYBE WE'LL DEAL WITH IT AT THE BOARD, IS THAT I GO BACK AND FORTH ON THIS ISSUE ABOUT UNDERREPRESENTED AREAS AND SO THAT GETS A PRIORITY. BECAUSE WE HAVE THIS LIMITED PERIOD OF TIME. THAT'S HOW MANY OF US ARE OPERATING. RIGHT? WHO KNOWS WHAT'S GOING TO HAPPEN AFTER THIS PERIOD OF TIME? ONE CAN MAKE THE ARGUMENT THAT AN AREA IN WHICH THERE'S BEEN A LOT OF ACTIVITY IS MAKING ADVANCES TO THE POINT WHERE, LIKE, THE NEXT PROJECT IS GOING TO BE THE BREAKTHROUGH PROJECT AS OPPOSED TO SOMETHING THAT IS WAY UNDERREPRESENTED, MEANING IT'S PROBABLY WAY BEHIND, NOT A LOT OF WORK HAS BEEN DONE ON IT, AND THAT'S GOING TO HAVE A LONGER TRAJECTORY TO GET TO

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THE POINT.

SO I JUST RAISE THIS AS A POINT TO THINK ABOUT. AND I DO GO BACK AND FORTH BECAUSE, OF COURSE, WE WANT TO SEE A BROAD PORTFOLIO. BUT, ROSA, AS YOU DESCRIBED, THERE IS A BROAD PORTFOLIO. BUT SOMETIMES SOMETHING THAT'S BEEN WORKED ON A LOT IS AT THE POINT OF ANOTHER BREAKTHROUGH WHICH MOVES IT TO LIKE ANOTHER LEVEL BECAUSE THERE'S BEEN SO MUCH WORK ON IT AND SHOULDN'T BE -- MAYBE SHOULDN'T BE PENALIZED BECAUSE THERE'S BEEN A LOT OF WORK DONE ON IT AND CIRM HAS FUNDED THAT. SO MAYBE IT'S FOOD FOR THOUGHT, BUT WE DO WANT BREAKTHROUGHS AND WE DO HAVE A TIMELINE, AND FOR SOMETHING STARTING FROM SCRATCH MAY NOT BE OPTIMAL. I'LL STOP THERE.

DR. CANET-AVILES: OKAY. I THINK WE CAN DEFINITELY TALK ABOUT THIS IN MARCH. I THINK IT'S A VERY GOOD POINT THAT YOU ARE RAISING. AND I THINK THE WHOLE POINT ABOUT THE DELIVERY, I THINK THAT THERE ARE MULTIPLE DELIVERY SYSTEMS TO THE CNS THAT WORK AND SEVERAL ARE ALREADY IN THE CLINIC. AND WE CONTINUE TO FUND AND SUPPORT THIS. BUT A NONVIRAL DELIVERY, WE PRIORITIZED IT AS A STRATEGIC PREFERENCE BECAUSE IT HAS THE POTENTIAL TO OVERCOME CONSTRAINTS THAT VIRAL SYSTEMS STILL FACE, LIKE REDOSING LIMITATIONS AND MANUFACTURING SCALABILITY

AND SUCH.

SO BASICALLY IT'S ABOUT PORTFOLIO BALANCE AND FUTURE OPTIONALITY, I COULD SAY, IN THIS CASE, BUT HAPPY TO DISCUSS FURTHER IN MARCH IF YOU WANT.

VICE CHAIR BONNEVILLE: I THINK WE SHOULD.

DR. CANET-AVILES: YEAH.

CHAIRMAN FISCHER-COLBRIE: I THINK THERE'S SOME OTHER QUESTIONS, RIGHT? WE CAN PROCEED.

DR. YVONNE CHEN: IS PUBLIC PARTICIPANT ALLOWED TO ASK A QUESTION RIGHT NOW?

MR. TOCHER: JUST A MINUTE. WE'RE FIRST GOING TO ENTERTAIN QUESTIONS FROM THE BOARD.

CHAIRMAN FISCHER-COLBRIE: ANY OTHER QUESTIONS FROM THE BOARD OR THE SCIENCE SUBCOMMITTEE?

MS. MANDAC: SO FOR MEMBERS OF THE PUBLIC, THE FLOOR IS OPEN AND WE'LL CALL ON YOU ONE BY ONE. YOU WILL SEE A TIMER ON THE TOP RIGHT-HAND CORNER OF YOUR ZOOM WINDOW. YOU WILL EACH HAVE THREE MINUTES. WE'LL START WITH DR. CHEN AND THEN MOVE ON TO DR. LIU-MICHAEL. DR. CHEN, THE FLOOR IS YOURS.

DR. YVONNE CHEN: GREAT. THANK YOU VERY MUCH. GOOD AFTERNOON. MY NAME IS YVONNE CHEN. I'M A PROFESSOR OF IMMUNOLOGY AT UCLA. I'D LIKE TO THANK THE SUBCOMMITTEE FOR YOUR TIME AS WELL AS THE

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CIRM STAFF FOR ALL OF YOUR EFFORT IN EXECUTING THE MISSIONS FOR CIRM.

I'M SPEAKING TODAY TO BRING TO YOUR ATTENTION AN IMPORTANT CONSEQUENCE OF THE PREFERENCE SYSTEM THAT DR. ROSA DISCUSSED WITH US IN DETAIL JUST NOW. AND SPECIFICALLY, IT'S A CONSEQUENCE THAT MAY OR MAY NOT HAVE BEEN INTENDED, AND IT WAS DESCRIBED AS PERCEPTION OF MODALITY BIAS IN DR. ROSA'S PRESENTATION. I'D LIKE TO DISCUSS WHY THIS IS NOT SIMPLY A PERCEPTION, BUT A REALITY.

BY VIRTUE OF LISTING SPECIFIC PREFERENCES IN TRIAGING APPLICATIONS BASED ON HOW MANY BOXES ONE COULD CHECK, THE PREFERENCE SYSTEM EFFECTIVELY ELIMINATES CERTAIN TREATMENT MODALITIES FROM CONSIDERATION. FOR EXAMPLE, FOR AN EX VIVO VIRALLY TRANSFUSED CAR-T CELL THERAPY, THE SAME KIND OF THERAPY THAT HAS BEEN APPROVED BY THE FDA AND HAS ACTUALLY TRANSFORMED TREATMENT FOR CANCER, SUCH AS B-CELL LYMPHOMA AND MULTIPLE MYELOMA, THERE ARE THREE BOXES THAT CAN NEVER BE CHECKED. THESE ARE IN VIVO, NONVIRAL, AND PLURIPOTENT STEM CELLS.

SO TO SIMPLIFY THE DISCUSSION, LET ME FOCUS JUST ON PDEV, BUT CLIN2 HAS THE SAME ISSUES. THERE'S A TOTAL OF SIX PREFERENCE BOXES IN PDEV. SO NOT BEING ABLE TO CHECK THREE OF THOSE BOXES MEANS

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CAR-T CELL THERAPY APPLICATIONS ARE IMMEDIATELY PUT AT A DISADVANTAGE THAT CAN NEVER BE OVERCOME REGARDLESS OF HOW STRONG THE SCIENCE IS.

AND IF THE THERAPY IS INTENDED FOR SOMETHING THAT'S NOT A CNS DISEASE, EVEN IF IT'S A HUGE UNMET MEDICAL NEED, SUCH AS LUNG CANCER, PANCREATIC CANCER, THAT'S ANOTHER BOX THAT WILL NEVER BE CHECKED. AND, THEREFORE, A PDEV APPLICATION FOR A CAR-T CELL THERAPY FOR LUNG CANCER, FOR EXAMPLE, WILL NEVER BE ABLE TO CHECK FOUR OUT OF SIX BOXES. SO THE MAXIMUM SCORE THAT CAN EVER BE ACHIEVED IS TWO, AND THAT DOOMS THE APPLICATION. IT WILL NEVER BE REVIEWED.

AND SO, AGAIN, WE'RE NOT EVEN CONSIDERING THE SCIENTIFIC MERIT. THIS IS SIMPLE BOX-CHECKING ARITHMETIC. AND IF WE LOOK AT THE LIST OF PDEV AND CLIN2 APPLICATIONS THAT WERE ACTUALLY FUNDED IN THE FIRST ROUND, THERE IS A COMPLETE ABSENCE OF CAR-T CELL THERAPIES. AND THIS IS WHY I SAY THIS IS NOT JUST A PERCEPTION. IT'S A REALITY OF THE PREFERENCE SYSTEM.

I SHOULD ALSO NOTE THAT, BASED ON THE TABLE THAT ROSA SHOWED ON SLIDE 11 OF HER DECK, WHICH IS A LITTLE DIFFERENT THAN THE TABLE THAT'S SHOWN IN THE RFA, ALL EX VIVO CAR-T CELL THERAPIES

THAT'S NOT FOR CNS DISEASES WILL AUTOMATICALLY BE ELIMINATED BECAUSE THE FIRST LINE IS AT LEAST ONE OF THE FOLLOWING. AND NONE OF THOSE THREE THINGS COULD BE CHECKED.

NOW, I UNDERSTAND RESOURCES ARE LIMITED, AND IT IS THE CIRM BOARD'S DISCRETION TO DECIDE, BUT I WANT TO POINT THIS OUT --

MS. MANDAC: DR. CHEN, YOUR TIME IS UP. NEXT WE HAVE DR. LIU-MICHAEL AND THEN DR. CHEN. DR. LIU-MICHAEL, THE FLOOR IS YOURS.

DR. LIU-MICHAEL: HI. THANK YOU SO MUCH, ROSA, FOR THE PRESENTATION AND ESPECIALLY FOR THE CLARIFICATION OF THE PREFERENCES. I'M QING LIU-MICHAEL FROM CITY OF HOPE. SO I SHARE THE SAME OPINION AS DR. PAT LEVITT, JUST TO CLARIFY ABOUT THE CIRM PREFERENCES UNDERREPRESENTED AREAS. IF YOU CAN IN THE FUTURE OR NOW CLARIFY THAT, THAT WOULD BE GREAT.

SO -- BECAUSE WE'VE BEEN, SIMILAR TO DR. YVONNE CHEN, CITY OF HOPE HAS BEEN SUBMITTING A LOT OF CANCER-RELATED PROPOSALS AND HAVE ALSO KNOWN APPLICANTS TO HAVE SUBMITTED CNS-RELATED DISEASE THAT GOT TURNED AWAY BECAUSE OF CIRM UNDERREPRESENTED AREAS. SO, YEAH, ANY MORE CLARIFICATION ON THAT, THAT WILL BE GREAT.

AND FINALLY, IF YOU CAN SHARE YOUR DECK SINCE IT'S DIFFERENT FROM THE ONE THAT'S SHARED ON THE WEBSITE, THAT WOULD BE GREAT. THANK YOU SO MUCH FOR THE PRESENTATION, AND THANK YOU ALL SO MUCH FOR YOUR WORK. THAT'S ALL.

MS. MANDAC: THANK YOU, DR. LIU-MICHAEL. DR. CHEN, THE FLOOR IS YOURS.

DR. JIA CHEN: HI, MEMBERS OF THE BOARD AND MEETING ATTENDEES. MY NAME IS JIA CHEN. I'M A CALIFORNIA RESIDENT AND PROFESSIONALLY AN ADMINISTRATOR FOR A RESEARCH CENTER AT THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND SUPPORT PHYSICIAN/SCIENTISTS WHO TREAT CANCER PATIENTS USING CELL/GENE THERAPIES. MY PROFESSIONAL ROLE PROVIDES ME WITH AN OPPORTUNITY TO SUPPORT CANCER PATIENTS ACROSS CALIFORNIA WHO HAVE GREATLY BENEFITED FROM CELL AND GENE THERAPIES.

IN THAT REGARD, I WANT TO FIRST THANK THE ENTIRE CIRM TEAM AND ICOC BOARD MEMBERS WHO WORK TIRELESSLY TO MAKE ALL THIS POSSIBLE. IN DOING MY JOB, I HAVE SEEN HOW IMPACTFUL CIRM HAS BEEN IN THE FIELD OF CELL AND GENE THERAPY. BUT I DO HAVE THREE OBSERVATIONS TO BRING TO THE ATTENTION OF THE ICOC SCIENCE SUBCOMMITTEE REGARDING THE IMPLEMENTATION OF THE CIRM STRATEGIC ALLOCATION FRAMEWORK THUS FAR.

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THE FIRST IS THAT THE NEW PREFERENCE SELECTION PROCESS INTENTIONALLY OR UNINTENTIONALLY ALGORITHMICALLY EXCLUDES MANY CELL AND GENE THERAPY APPROACHES THAT HAVE DEMONSTRATED TO BE SAFE AND CLINICALLY EFFICACIOUS FOR PATIENTS. MANY OF THESE PHYSICIAN/SCIENTISTS LEADING SUCCESSFUL CELL THERAPY TRIALS ARE COMPLETING THEIR MULTIYEAR EFFORTS TO TRANSLATE CELL THERAPIES INTO FDA IND APPLICATIONS ARE SUDDENLY NOT HAVING THEIR CIRM APPLICATIONS REVIEWED SCIENTIFICALLY SINCE IMPLEMENTATION OF THE STRATEGIC ALLOCATION FRAMEWORK.

THE SECOND IS TO POINT OUT A PRACTICAL FACT, THAT CIRM-FUNDED CELL AND GENE RESEARCH PROGRAMS WHICH MIGHT BE MEETING MILESTONES AND SHOWING SUCCESS HAVE VERY LITTLE, IF ANY, FUNDING ALTERNATIVE TO CONTINUE ON THE PATH TOWARDS CLINICAL TRIAL OUTSIDE OF CIRM. THIS IS PARTICULARLY POIGNANT IN THE CURRENT RESEARCH FUNDING ENVIRONMENT IN OUR COUNTRY THAT IS DRASTICALLY DIFFERENT COMPARED TO WHEN THE STRATEGIC ALLOCATION FRAMEWORK WAS BEING DEVELOPED AND OPTIMIZED BY CIRM ABOUT TWO YEARS AGO.

MY LAST COMMENT IS THAT AS A CALIFORNIA TAXPAYER, I HAVE CONCERNS FOR A CIRM FUNDING PREFERENCE LIST THAT SKEWS THE FLOW OF STATE FUNDS

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TO PRIVATE COMPANIES INSTEAD OF AN APPLICATION SELECTION PROCESS THAT IS SOLELY BASED ON SCIENTIFIC MERIT. I THINK IT'S BECAUSE TWO OF THE EIGHT CRITERIA FOR CLIN2, BEFORE AN APPLICATION WILL BE SUBMITTED FOR SCIENTIFIC REVIEW, ARE AN ACCELERATED FDA DESIGNATION OR A PIVOTAL TRIAL, WHICH WOULD REQUIRE OR NEED ANTICIPATION OF A COMMERCIAL ENTITY TO APPLY AT THE FDA. TWO OUT OF EIGHT CRITERIA IS A STRONG SKEWING SELECTION FOR THE CIRM AWARD TOWARDS PRIVATE COMPANIES.

I THANK YOU FOR ALL YOUR ATTENTION.

MS. MANDAC: THANK YOU SO MUCH, DR. CHEN. MARK, THERE ARE NO ADDITIONAL HANDS RAISED. BACK TO YOU.

CHAIRMAN FISCHER-COLBRIE: GREAT. I THINK IT'S IMPORTANT FOR US TO TAKE INTO CONSIDERATION THE COMMENTS FROM THE PUBLIC IN THE ONGOING ASSESSMENT OF THE PROGRAM AND THE PROCESS. AND WE WILL CONTINUE TO EVALUATE THE IMPORTANT FEEDBACK AND CONSIDERATIONS AS WE GO THROUGH THIS EFFORT. AND WE WILL FOLLOW UP INTERNALLY WITH THE CIRM TEAM AROUND THAT PROCESS, AND THERE WILL BE FURTHER DISCUSSION ABOUT HOW WE MOVE FORWARD.

ROSA, I DON'T KNOW IF YOU WANT TO ADD SOME ADDITIONAL COMMENTARY TO THAT.

DR. CANET-AVILES: NO. THANK YOU, MARK.

CHAIRMAN FISCHER-COLBRIE: OKAY. THANK YOU VERY MUCH. WE APPRECIATE THE FEEDBACK. AND UNLESS THERE ARE ANY OTHER COMMENTS, I THINK WE CAN CONCLUDE THE MEETING OR ANY OTHER COMMENTS OR FEEDBACK? OKAY. THERE BEING NONE, I APPRECIATE EVERYBODY'S TIME. AND WE ARE EXCITED ABOUT CONTINUING TO TRY TO MAXIMIZE THE OPPORTUNITIES FOR LEVERAGING AND ACCELERATING SCIENCE. SO WE LOOK FORWARD TO WORKING HARD AS ALWAYS TO ACHIEVE THAT GOAL. SO THANK YOU.

VICE CHAIR BONNEVILLE: THANK YOU, EVERYONE.

(THE MEETING WAS THEN CONCLUDED AT 2:14 P.M.)

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REPORTER'S CERTIFICATE

I, BETH C. DRAIN, A CERTIFIED SHORTHAND REPORTER IN AND FOR THE STATE OF CALIFORNIA, HEREBY CERTIFY THAT THE FOREGOING TRANSCRIPT OF THE VIRTUAL PROCEEDINGS BEFORE THE SCIENCE SUBCOMMITTEE OF THE INDEPENDENT CITIZEN'S OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF ITS REGULAR MEETING HELD ON JANUARY 14, 2026, WAS HELD AS HEREIN APPEARS AND THAT THIS IS THE ORIGINAL TRANSCRIPT THEREOF AND THAT THE STATEMENTS THAT APPEAR IN THIS TRANSCRIPT WERE REPORTED STENOGRAPHICALLY BY ME AND TRANSCRIBED BY ME. I ALSO CERTIFY THAT THIS TRANSCRIPT IS A TRUE AND ACCURATE RECORD OF THE PROCEEDING.

BETH C. DRAIN, CA CSR 7152
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