BEFORE THE
TASK FORCE ON NEUROSCIENCE 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: MARCH 13, 2023
10 A.M.

REPORTER: BETH C. DRAIN, CA CSR
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I N D E X

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MARCH 13, 2023; 10 A.M.

CHAIRMAN GOLDSTEIN: THANK YOU. ALL RIGHT. LET ME CALL US TO ORDER, AND THE FIRST ORDER OF BUSINESS IS FOR MARIANNE TO CALL THE ROLL.

MS. DEQUINA-VILLABLANCA: LEONDRA CLARK-HARVEY. MARIA BONNEVILLE.

VICE CHAIR BONNEVILLE: PRESENT.

MS. DEQUINA-VILLABLANCA: MARK FISCHER-COLBRIE.

DR. FISCHER-COLBRIE: HERE.

MS. DEQUINA-VILLABLANCA: FRED FISHER. I'LL COME BACK TO HIM.

JUDY GASSON.

DR. GASSON: HERE.

MS. DEQUINA-VILLABLANCA: LARRY GOLDSTEIN.

CHAIRMAN GOLDSTEIN: I'M HERE.

MS. DEQUINA-VILLABLANCA: DAVID HIGGINS.

DR. HIGGINS: HERE.

MS. DEQUINA-VILLABLANCA: STEVE JUELSGAARD.

MR. JUELSGAARD: HERE.

MS. DEQUINA-VILLABLANCA: PAT LEVITT.

DR. LEVITT: HERE.

MS. DEQUINA-VILLABLANCA: LAUREN

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MILLER-ROGEN. AL ROWLETT.

MR. ROWLETT: HERE.

MS. DEQUINA-VILLABLANCA: MARVIN SOUTHARD.

DR. SOUTHARD: PRESENT.

MS. DEQUINA-VILLABLANCA: JONATHAN THOMAS.

CHAIRMAN THOMAS: HERE.

MS. DEQUINA-VILLABLANCA: KEITH YAMAMOTO.

AND FRED FISHER. HE IS ON, BUT I KNOW HE DOES HAVE CONNECTIVITY ISSUES, BUT HE IS ON.

CHAIRMAN GOLDSTEIN: OKAY. SO HERE'S WHAT I'LL DO TO GET US STARTED. I WANT TO GIVE YOU A QUICK SUMMARY OF THE LAST MEETING AND A SUMMARY OF A PROPOSED PLAN FOR US MOVING FORWARD. AND THEN I'LL TAKE THINGS SLIGHTLY OUT OF ORDER AND HAND THE MICROPHONE OVER TO ROSA WHO'S GOT SORT OF A BIRD'S-EYE VIEW OF A CONCEPT PLAN THAT SHE'S WORKING ON THAT I THINK FITS PRETTY NICELY WITH THE DIRECTION WE ARE GOING.

SO YOU MAY RECALL THAT AT THE LAST MEETING WE AGREED TO FOCUS OUR INITIAL PLANNING EFFORTS ON NEUROPSYCHIATRIC DISEASES, WHICH WE REALIZE FROM A VERY HELPFUL PORTFOLIO ANALYSIS FROM THE CIRM TEAM THAT WE BASICALLY HAVE NO INVESTMENT IN NEUROPSYCHIATRIC DISORDERS, ALTHOUGH WE HAVE LOTS OF INVESTMENTS IN DIFFERENT SORTS OF NEURODEGENERATIVE

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DISORDERS. AND SO THAT'S IN PART WHERE THE INITIAL FOCUS ON NEUROPSYCHIATRIC DISORDERS COMES FROM, PLUS THE SENSE OF SOME OF US THAT IT MAY BE A GOOD, MANIPULABLE SYSTEM TO DEVELOP FOR UNDERSTANDING MECHANISM AND PERHAPS FOR DEVELOPING THERAPIES.

MOVING FORWARD, WHAT I'M GOING TO SUGGEST THAT WE DO IS DO A BIT OF EDUCATING OURSELVES ABOUT WHAT IS AND ISN'T KNOWN IN THE AREA AND LET THAT INFORM OUR DEVELOPMENT OF SUGGESTED CONCEPT PLANS AND WHERE WE THINK DEVELOPMENT EFFORTS OUGHT TO BE FOCUSED.

THAT WILL GIVE US FIVE OR SIX MEETINGS PROBABLY. I'LL SEND OUT A PROPOSED SCHEDULE SHORTLY. AND ONE OF THE IDEAS WE HAVE MOVING FORWARD IS THAT WE SHOULD BE LOOKING AT HELPING ROSA OR VICE PRESIDENT CANET-AVILES, AS I'VE JUST LEARNED, TO PREPARE A CONCEPT PLAN BASED ON OUR EDUCATION AND DELIBERATIONS THAT OCCUR BETWEEN NOW AND JUNE.

SO UNLESS THERE ARE QUESTIONS, I'LL TAKE THOSE NOW IF THERE ARE ANY. I'LL ALSO POINT OUT THAT I SAW DR. NEALE HAS JOINED US ALREADY. THANK YOU FOR PARTICIPATING, DR. NEALE. AND I DON'T KNOW IF DR. SEBAT IS WITH US YET OR NOT. HE MIGHT BE ONE OF THOSE PHONE NUMBERS. I CAN'T TELL. BUT THEY

WILL BE GIVING US SHORT PRESENTATIONS THIS MORNING WHICH WE'LL GET TO SHORTLY. SO UNLESS THERE'S ANYTHING BURNING, LET ME TURN THE MICROPHONE TO OVER ROSA TO LAY OUT A HIGH LEVEL SUMMARY OF A PROPOSED CONCEPT PLAN THAT IS IN DEVELOPMENT.

DR. CANET-AVILES: THANK YOU, DR. GOLDSTEIN. I AM GOING TO SEE -- CAN YOU SEE MY FULL SCREEN?

CHAIRMAN GOLDSTEIN: YEP.

DR. CANET-AVILES: WONDERFUL.

SO AS DR. GOLDSTEIN MENTIONED, THE STAFF AT CIRM HAS BEEN WORKING ON WHAT COULD BE A BIRD'S-EYE VIEW OF A CONCEPT THAT COULD FIT WELL WITH WHAT THE BOARD IS THINKING, IS CURRENTLY THINKING, COULD BE. SO I AM GOING TO GO OVER A LITTLE BIT OF BACKGROUND, HISTORICAL BACKGROUND OF WHERE DOES THAT COME FROM? I'LL DO A LITTLE BIT OF -- I'LL SHOW A PORTFOLIO ANALYSIS THAT JUSTIFIES WHAT WE ARE THINKING. AND I WILL GO INTO A VERY HIGH LEVEL OVERVIEW OF THE PLAN.

SO THIS SLIDE PROVIDES A FRAME FOR THE BACKGROUND AND THE RATIONALE FOR THE CONCEPTUALIZATION OF THIS POTENTIAL CONCEPT. THE VISION FOR THIS NEURODISCOVERY STRATEGY HAS BEEN INFORMED BY MULTIPLE LAYERS OF STAKEHOLDER

DISCUSSIONS AND INPUT THAT STARTED EVEN PRIOR TO THE PASSAGE OF PROPOSITION 14 OVER THE PAST TWO YEARS AS OUTLINED IN THIS TIME LINE CHART.

THERE ARE FOUR KEY TAKEAWAYS OUT OF ALL THESE MEETINGS HIGH LEVEL. THERE ARE FOUR KEY TAKEAWAYS I'M GOING TO GO OVER IN THE NEXT SLIDE THAT LEAD TO WHERE WE ARE TODAY, WHICH IS THE THINKING ABOUT THE DEVELOPMENT OF THIS CONCEPT.

THE FIRST THREE TAKEAWAYS WERE DIRECTLY CAPTURED WITHIN OUR FIRST STRATEGIC THEME OF THE ADVANCE WORLD-CLASS SCIENCE. SO IN THE STRATEGIC THEME FOR ADVANCING WORLD-CLASS SCIENCE, WE ARE CALLING FOR A CONSORTIUM APPROACH THAT WILL ALLOW US TO LEVERAGE GENOMICS, BIG DATA, NOVEL STEM CELL MODELS, PATIENT DATA AND COLLABORATION, PROMOTE KNOWLEDGE SHARING, AND EXPAND SHAREABLE RESOURCES.

NOW, THE SCIENTIFIC ADVISORY BOARD ALSO PROVIDED FEEDBACK WITH REGARDS TO THE DIRECTIONS IN WHICH THE NEURO STRATEGY SHOULD GO BY POINTING TO THE EXISTENCE OF STILL MAJOR GAPS IN OUR UNDERSTANDING OF THE MECHANISMS UNDERLYING NORMAL AND DISEASE PROCESSES IN THE BRAIN. THIS IS NOT TO SAY THAT THERE ARE NOT OTHER IMPORTANT GAPS TO TACKLE IN THE OVERALL NEURO STRATEGY; BUT FOR THE FIRST PHASE OF THE NEURO STRATEGY, THE MAIN FOCUS IN

OUR VIEW AT THE LEVEL OF DISCOVERY SHOULD BE AROUND FOUNDATIONAL WORK AND UNDERSTANDING NORMAL AND DISEASE MECHANISMS. AND IMPORTANTLY, THE APPROACH SHOULD BE BY LEVERAGING ALL THE PIECES THAT WE ARE PUTTING TOGETHER THROUGH THE ADVANCE WORLD-CLASS SCIENCE.

NOW, HOW MUCH OF THIS TYPE OF RESEARCH, UNDERSTANDING OF THE MECHANISMS UNDERLYING NORMAL AND DISEASE PROCESSES IN THE BRAIN, INCLUDING NEUROPSYCHIATRIC, HAS CIRM FUNDED SO FAR. THIS IS LIKE WE CAN SEE THAT WE FUNDED AT THE DISCOVERY LEVEL UP TO AROUND $1.1 BILLION IN DISCOVERY. SO OF THAT, HOW MUCH IS NEURO AND HOW MUCH IS MECHANISMS OF DISEASE? FOR THAT, WE ARE PROVIDING A COUPLE MORE SLIDES.

AS YOU CAN SEE, OF THE INVESTMENTS THAT WE HAVE MADE IN DISCOVERY, WE HAVE A LARGE PERCENTAGE, ABOUT 33 PERCENT, OF AWARDS THAT PERTAIN TO THE NEUROSCIENCE PORTFOLIO. AS YOU RECALL, MY COLLEAGUE, ABLA CREASEY, THE OTHER DAY PRESENTED ON THE TRAN AND CLIN. THIS IS FOR DISCOVERY. OF THOSE 33 PERCENT, THIS SLIDE SHOWS HOW ARE THEY DIVIDED IN THE DIFFERENT ETIOLOGIES. 37 PERCENT OF THE FUNDED AWARDS HAVE BEEN FOCUSED ON NEURODEGENERATIVE DISEASES. AND THEN WE HAVE ABOUT 11 PERCENT OF EYE

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DISEASES; 7 PERCENT BRAIN CANCER; NEUROTRAUMA, 17 PERCENT; NEURODEVELOPMENTAL, 12 PERCENT; AND THEN OTHER, WHICH INCLUDES A NUMBER OF PROJECTS IN EARLY STAGE IN BASIC RESEARCH GRANTS, THAT SOME OF THEM ARE JUST FOCUSING ON STUDYING DIFFERENTIATION OF STEM CELLS OR LIKE ZIKA VIRUS OR NEUROPATHY OR SOME PEDIATRIC METABOLIC DISORDERS THAT WE PUT THEM IN THE 16 PERCENT.

NOW, IMPORTANTLY, FOR TODAY'S TASK FORCE DISCUSSION, IT'S IMPORTANT TO REMARK THAT CIRM HAS NOT REALLY FUNDED MUCH RESEARCH IN NEUROPSYCHIATRIC DISEASES, SUCH AS SCHIZOPHRENIA, ADDICTION, BIPOLAR, LARGELY BECAUSE WE HAVE NOT RECEIVED MANY APPLICATIONS. WE HAVE A COUPLE OF -- WE HAVE SOME RESEARCH AROUND SCHIZOPHRENIA THAT CAME OUT OF DR. FRED GAGES'S LAB WITH KRISTIN BRENNAND, WHO'S NOW AT THE BROAD -- SORRY -- AT YALE, BUT WE HAVE NOT FUNDED MUCH NEUROPSYCHIATRIC RESEARCH.

NOW, ONE COULD EXPECT WITH SUCH A LARGE PERCENTAGE OF RESEARCH FOCUSED ON NEURO THAT WE WOULD HAVE MORE CURES. ONE OF THE ISSUES, AND THIS RELATES TO THE SCIENTIFIC ADVISORY BOARD RECOMMENDATION, IS THE LACK OF OUR UNDERSTANDING OF THE MECHANISMS UNDERLYING THOSE DISEASES AND PROCESSES IN THE BRAIN. AND IN ORDER TO HIGHLIGHT

THIS, OF ALL THE GRANTS, A VERY SMALL PERCENTAGE, ABOUT 4 PERCENT OF THE GRANTS HAVE BEEN FOCUSED SO FAR IN NEURODISEASE MECHANISMS. THIS CLEARLY POINTS OUT TO A GAP IN OUR FUNDING THAT IS ESSENTIAL AND MIGHT BE TO FULFILL CIRM'S MISSION.

SO THE NEXT SLIDE IS GOING TO PROVIDE AN OVERVIEW OF THE POTENTIAL FORMAT FOR DRIVING A NEURO-BASED DISCOVERY PROGRAM THAT COULD ACTUALLY PUT TOGETHER ALL THE ELEMENTS THAT WE ARE PROPOSING AND THAT ALSO WE ARE FUNDING THROUGH THE FIRST THEME OF OUR STRATEGIC PLAN.

SO THIS ULTIMATELY COULD BE A MULTILAYERED PROPOSAL THAT PULLS ALL EXISTING PIECES TOGETHER IN SERVICE OF THE OVERALL NEURO STRATEGY AND IS CONSISTENT WITH THE FEEDBACK RECEIVED AND IMPORTANTLY WITH PROPOSITION 14'S MANDATE. THE GOAL COULD BE TO DEVELOP A FRAMEWORK THAT COULD HELP US ACCELERATE THE PACE OF DISCOVERY AND INFORM THE PATHS TO CURE NEURODISEASES WITH AN INITIAL FOCUS IN FINDING NEW CLUES THROUGH THESE NEURODISCOVERY MULTIDISCIPLINARY TEAMS THAT WE'LL TALK ABOUT IN THE NEXT SLIDES AND THAT LEVERAGE THE WORK FROM OTHER CONSORTIA.

SO WE COULD HAVE THESE NEURO MULTIDISCIPLINARY TEAMS THAT COULD GENERATE DATA AND

COULD BE ABLE TO LEVERAGE DATA FROM OTHER CONSORTIA. AND IN ORDER MAXIMIZE THE INVESTMENT, WE COULD DO THESE THROUGH A DATA COORDINATING AND MANAGEMENT CENTER THAT WE COULD ALSO FUND THROUGH CIRM. AND WE COULD ALSO LEVERAGE -- SO THIS DATA COORDINATING AND MANAGEMENT CENTER COULD HAVE A KNOWLEDGE PLATFORM AND COULD ALLOW US TO LEVERAGE THE DATA THAT COMES FROM THE MULTIDISCIPLINARY TEAMS TOGETHER WITH THE EXTERNAL CONSORTIA DATA FROM OTHER PLATFORMS.

AND EVENTUALLY WE COULD ALSO COORDINATE AND LEVERAGE THE SHARED RESOURCE LAB MODELS, THE NEUROSCIENCE AND NEURO MODELS LIKE IPS MODELS. ORGANOID MODELS, AS YOU KNOW, YOU APPROVED A CONCEPT THAT WE ARE GOING TO LAUNCH SHORTLY THE RFA'S FOR. SO WE COULD LEVERAGE THOSE MODELS AS WELL. AND WE COULD ALSO LEVERAGE FUNDING FROM OUR DISCOVERY PROGRAMS, AND WE COULD PULL ALSO FROM THE TRAINING AND EDUCATION WORKFORCE DEVELOPMENT TO FEED INTO THIS KIND OF PROGRAM.

SO THE CONNECTION AND THE VISION OF THE NEURODISCOVERY AS PART OF THE NEURO STRATEGY AND FEEDING WITH THIS DATA COORDINATING AND MANAGEMENT CENTER CONSORTIA COLLABORATIVE ECOSYSTEM AND COMPETING COMPETENCY HUBS COULD COORDINATE A SERIES OF ACTIVITIES THAT COULD END UP IN THIS

COLLABORATIVE OPEN SCIENCE COMMUNITY WITH ULTIMATELY THE AIM COULD BE TO IDENTIFY, THROUGH THE DISCOVERY OF NEW MECHANISMS OF DISEASE, IDENTIFY AND VALIDATE THE MOST PROMISING BIOLOGICAL TARGETS FOR THERAPEUTICS. SO THESE ARE ALIGNED WITH FEEDING INTO OUR TRANSLATIONAL AND OUR CLINICAL PIPELINE.

NOW, WHAT COULD BE THE OBJECTIVES OF THESE NEURODISCOVERY MULTIDISCIPLINARY TEAMS CONCEPT? THIS RFA, THIS COULD BE TO START IMPLEMENTING THIS STRATEGY. WE COULD HAVE FIVE OBJECTIVES. THE FIRST WOULD BE TO FOCUS ON FOUNDATIONAL BIOLOGY TO ADVANCE THE FUNDAMENTAL UNDERSTANDING OF BIOLOGY ACROSS NEUROPSYCHIATRIC. IT LOOKS LIKE AT THE BEGINNING WE HAD NEURODEGENERATIVE, NEUROPSYCHIATRIC, NEURODEVELOPMENTAL DISEASES. THE DISCUSSIONS FROM THE TASK FORCE ARE POINTING OUT THAT WE ARE GOING TO BE FOCUSED ON NEUROPSYCHIATRIC. SO THE FOCUS COULD BE UNDERSTANDING THE FUNDAMENTAL SCIENCE OF NEUROPSYCHIATRIC DISORDERS THROUGH FOUNDATIONAL SYSTEMS TO EXPLORE NEW PATHWAYS, TARGETS, BIOMARKERS, AND ALSO TO RECONCEPTUALIZE NEURODISEASE AS A BROAD DISEASE CLASS INVOLVING MORE THAN THE BRAIN AND NEURONS BECAUSE THERE ARE OTHER SYSTEMS LIKE THE IMMUNE SYSTEM, THE GUT MICROBIOME SYSTEM INVOLVED IN THIS.

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THIS IS A COLLABORATION. WE WOULD LIKE TO INCENTIVIZE -- ANOTHER OBJECTIVE COULD BE TO INCENTIVIZE AND CATALYZE AN OPEN COLLABORATIVE MULTIDISCIPLINARY SCIENCE THAT ALSO COLLABORATES WITH THE DATA ECOSYSTEM. AND THIS COULD BE INTEGRALLY DEPENDENT ON A DATA INFRASTRUCTURE, DATA COORDINATING AND MANAGEMENT CENTER CONCEPT, AND THE DATA SHARING AND MANAGEMENT IMPLEMENTATION THAT WE ARE DOING.

THE THIRD ONE COULD BE TO MOTIVATE AND SUPPORT INNOVATIVE, BOLD, TRANSFORMATIVE NEW IDEAS AND TOOLS THAT ADDRESS FUNDAMENTAL CHALLENGES IN CNS DISEASE BIOLOGY. WE ALL KNOW ABOUT OPTIGENETICS, FOR EXAMPLE, BUT HOW ABOUT OTHER TECHNOLOGIES THAT WE COULD SUPPORT THE DEVELOPMENT THAT COULD ACTUALLY BE LEVERAGED WITH THIS KIND OF EFFORT.

AND LASTLY -- SORRY -- THE FOURTH IS TO ATTRACT NEW TALENT AND EXPERTISE INTO THE FIELDS AND ALSO TO ATTRACT DIFFERENT MULTIDISCIPLINARY TYPE OF EFFORTS. SO WE NOT ONLY WANT STEM CELL SCIENTISTS, BUT WE WOULD LIKE TO HAVE CLINICIANS, NEURO-IMMUNOLOGISTS, COMPUTATIONAL BIOLOGISTS. THIS SHOULD BE THE KIND OF EXPERTISE THAT WE WANT, WHICH IS IN THE SECOND POINT AS MULTIDISCIPLINARY, BUT ALSO NEW TALENT.

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AND THEN FINALLY, LEVERAGING AND CONNECTING WITH CIRM'S EXISTING INFRASTRUCTURE OF PROGRAMS, WHICH IS WHAT I WAS MENTIONING BEFORE IN TERMS OF LEVERAGING THE SHARED RESOURCE LABS, LEVERAGING THE DISCOVERY RESEARCH THAT WE HAVE, LEVERAGING EDUCATION, THE DATA COORDINATING MANAGEMENT, ET CETERA. SO I THINK IT'S IMPORTANT TO HAVE THIS HOLISTIC ECOSYSTEM OVERVIEW AS WE ARE PROPOSING THIS NEW CONCEPT, HOW WILL IT PLAY WITH EVERYTHING ELSE.

SO THE STRUCTURE THAT WE ARE THINKING ABOUT FOR THIS NEW CONCEPT COULD BE TO HAVE A FIRST PHASE THAT COULD HAVE A PLANNING AWARD. AND THE GOAL COULD BE TO GATHER IN THE FIRST SIX MONTHS OF THESE AWARDS TO GATHER THE TEAM AND DEVELOP THE PROPOSAL. THE OBJECTIVE OF THIS PLANNING AWARD IS TO ENABLE THE PRINCIPAL INVESTIGATOR TO RECRUIT A MULTIDISCIPLINARY TEAM AND TO UNLEASH THE TEAM TO DEVELOP THE CONTENT MANAGEMENT AND ADMINISTRATION OF THE PROPOSED MULTIDISCIPLINARY NEURODISCOVERY RESEARCH.

BUT IMPORTANTLY, SOMETHING THAT WE WANTED TO MAKE SURE, BECAUSE THIS WOULD ALL BE COMING AS WE ARE DEVELOPING DATA COORDINATING AND MANAGEMENT CENTER, IS THAT THESE TEAMS COULD BE REACHING OUT TO

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OTHER GROUPS AND CONSORTIA THAT COULD BE EITHER SUPPLEMENTING THEIR RESEARCH OR COLLABORATING. AND THEY COULD PROPOSE THAT IN THEIR AWARD, WHICH CONSORTIA COULD THEY BE ACTUALLY TAPPING INTO SO THAT CIRM CAN START DISCUSSING WITH THOSE CONSORTIA SO WE CAN BRING THEM TO THE TABLE AS THE PROJECT IS BEING DEVELOPED SO WE ARE READY FOR THE TIME OF IMPLEMENTATION.

THE SECOND PHASE OF THE RESEARCH AWARD COULD BE PROJECT IMPLEMENTATION AND COLLABORATION. AND THIS IS SOMETHING THAT NEEDS TO BE FLESHED OUT THE TIMING, ET CETERA, BUT OVERALL THIS IS A POTENTIAL STRUCTURE FOR THIS NETWORK THAT WE ARE THINKING.

AND WITH THAT, I WOULD LIKE TO THANK DR. GOLDSTEIN FOR HIS INVALUABLE INPUT. AND I'D LIKE TO THANK THE MEMBERS OF THE BOARD FOR ALLOWING ME TO PRESENT CIRM'S THINKING AROUND THIS. THANK YOU.

CHAIRMAN GOLDSTEIN: EXCELLENT, ROSA. THANK YOU VERY MUCH.

I GUESS I HAVE A COUPLE OF QUESTIONS, AND THEN I'LL THROW IT OPEN TO THE GROUP FOR QUESTIONS AND DISCUSSION.

I THINK ONE OF THE QUESTIONS IS HISTORICAL. WHEN WE SAY WE HAVEN'T FUNDED ANY

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NEUROPSYCHIATRIC APPLICATIONS, IS THAT BECAUSE WE DON'T GET ANY NEUROPSYCHIATRIC APPLICATIONS OR BECAUSE THEY HAVEN'T FARED WELL IN COMPETITION WITH NEURODEGENERATIVE OR NEURODEVELOPMENTAL OR WHATEVER?

DR. CANET-AVILES: WE HAVEN'T GOTTEN MANY ACTUALLY IN PROPORTION TO THE REST OF TYPE OF APPLICATIONS, BUT WE HAVE ALSO NOT BEEN CALLING SPECIFICALLY FOR THEM. SO I THINK THAT -- WHEN WE FINALIZED THE PORTFOLIO, WE WERE CALLING FOR MECHANISMS OF STEM CELL AND REGENERATIVE MEDICINE PLURIPOTENCY AND ALL OF THIS, BUT WE WERE NOT CALLING SPECIFICALLY FOR DISEASE MECHANISMS AND NOT SPECIFICALLY FOR PSYCHIATRIC.

SO ON PSYCHIATRIC, THE MODELING HAS BEEN MORE CHALLENGING. SO THERE WERE LESS APPLICATIONS.

CHAIRMAN GOLDSTEIN: OKAY. GOOD. SO WOULD YOU RECOMMEND THAT WE CALL OUT A SEPARATE CALL FOR PROPOSALS FOR NEUROPSYCHIATRIC, OR SHOULD WE WAIT AND SEE WHETHER THEY OCCUPY A SIGNIFICANT FRACTION OF A GENERAL CALL?

AND I GUESS THE RELATED QUESTION IS IS THERE SOME WAY TO ADVERTISE THAT WE ARE INTERESTED IN GETTING THESE APPLICATIONS, AND WE THINK THAT THE TIME IS RIGHT TO MAKE AN INVESTMENT HERE?

DR. CANET-AVILES: SO THANK YOU, DR.

GOLDSTEIN. TO THE FIRST QUESTION, I THINK THE KEY IS TO CALL OUT FOR A SPECIFIC, AND THAT IS LINKED TO THE ANSWER TO THE SECOND QUESTION, THAT EFFORTS CAN BE MADE. IN FACT, TODAY I HAPPENED TO BE AT THE NEUROSCIENCE FORUM OF THE NATIONAL ACADEMIES. AND THEY ARE VERY INTERESTED TO HEAR WHAT CIRM IS DOING. SO ONCE WE HAVE A PLAN WE CAN PRESENT, AND THERE ARE MANY DIVERSE STAKEHOLDERS LIKE THE NATIONAL INSTITUTES OF MENTAL HEALTH AND OTHERS THAT COULD BE INTERESTING TO SEE WHAT ARE WE DOING AND HOW CAN WE COLLABORATE AND LEVERAGE OUR EFFORTS.

CHAIRMAN GOLDSTEIN: YEAH. THAT'S REALLY GOOD NEWS BECAUSE I THINK, IN ADDITION TO DEVELOPING MODELS, THERE HAS BEEN INTEREST EXPRESSED TO ME OFF LINE FROM A GROUP AT UCLA AND UCSF THAT, IN ADDITION TO DEVELOPING CELLULAR MODELS TO STUDY MECHANISM, THEIR VIEW IS THAT THE STUDY OF DIFFERENT POPULATIONS FOR GENETIC ELEMENTS THAT MAY DRIVE DISEASE IS REALLY NOT YET BROAD ENOUGH. AND IT MIGHT BE THE CASE THAT WE WOULD WANT TO ENGAGE IN SOME SORT OF COLLABORATION WITH NIMH AND OTHER ORGANIZATIONS TRYING TO MAKE PROGRESS IN THIS RATHER CHALLENGING AREA. SO --

DR. CANET-AVILES: EXACTLY. AND PROBABLY DR. NEALE MIGHT TALK ABOUT THAT. I WAS TALKING TO

DR. HYMAN HERE AT THE NEUROSCIENCE FORUM. SO, YEAH, HE MIGHT BE SPEAKING TO THAT.

CHAIRMAN GOLDSTEIN: OTHER QUESTIONS OR DISCUSSION BEFORE WE BRING IN OUR GUESTS? J.T.

CHAIRMAN THOMAS: ROSA, THANK YOU VERY MUCH FOR THAT EXCELLENT PRESENTATION AND CONCEPTUAL GAME PLAN HERE GOING FORWARD. I THINK IT MAKES A LOT OF SENSE.

I HAVE A QUESTION THAT'S A BIT OF A FOLLOW-ON TO WHAT LARRY JUST ASKED, WHICH IS, AND I TOO HEARD CONVERSATIONS INVOLVING UCLA AND UCSF, BUT AS A GENERAL MATTER, DO WE HAVE A SENSE FOR HOW MUCH RESEARCH IN THE STATE, THROUGHOUT THE STATE, BESIDES THOSE INSTITUTIONS IS CURRENTLY BEING DONE IN THIS SPACE AT THIS POINT?

DR. CANET-AVILES: WE HAVE A SENSE, J.T. I COULD ACTUALLY BRING BACK THE DATA. I DON'T HAVE RIGHT IT NOW ON THE TIP OF MY HEAD, BUT I WILL SEND IT BACK. WE DO HAVE BECAUSE WE HAVE A LOT OF CONSULTATIONS AT THE EARLY DISCOVERY RESEARCH OF PEOPLE ASKING BESIDES NEUROPSYCHIATRIC, NEURODEVELOPMENTAL GO TOGETHER AND THERE'S A LOT OR RESEARCH AROUND NEURODEVELOPMENTAL THAT COULD ACTUALLY ALSO BE PART OF THE SCOPE OF THIS.

WHEN WE THINK ABOUT ADDICTION AS WELL,

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IT'S ALSO MODELING, AND WORK AROUND THAT COULD BE PART OF WHAT WE WOULD BE FUNDING. SO YEAH.

CHAIRMAN THOMAS: THANK YOU.

CHAIRMAN GOLDSTEIN: NEXT UP, PAT.

DR. LEVITT: THANKS, ROSA. VERY NICE AND MULTIDISCIPLINARY PLAN AND TEAM FORGING A GREAT IDEA.

I GUESS I HAVE TWO COMMENTS. ONE, I GUESS IT'S OBVIOUS TO EVERYBODY THAT THE FRAMEWORK AROUND WHICH AN RFA WOULD BE ISSUED BASED ON THE CHARGE THAT CIRM HAS IN TERMS OF WHAT IT WILL FUND AND IT WON'T FUND WILL BE VERY IMPORTANT BECAUSE THERE'S A LOT OF WORK IN THIS SPACE THAT WOULDN'T NECESSARILY FALL IN THE RUBRIC OF SUPPORT BY CIRM. AND SO WE -- PROBABLY A GREAT IDEA, THE QUESTION ABOUT HOW MUCH -- THERE'S A LOT OF RESEARCH GOING ON IN THE STATE OF CALIFORNIA. SOME OF IT IS NEUROIMAGING, SOME OF IT IS GENETICS THAT LIKELY WOULDN'T FALL INTO THE RUBRIC. I THINK THAT WOULD BE OPEN FOR DISCUSSION, I GUESS, TO MAKE SURE THAT IT'S ALIGNED WITH THE CHARGES OVERALL.

THE SECOND COMMENT IS THAT NIH NOW HAS ISSUED AN EDICT TO ALL OF US WHO ARE FUNDED BY NIH ABOUT DATA SHARING AND DATA MANAGEMENT. AND I THINK WE CAN PIGGYBACK ON THAT BECAUSE IT'S

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EXTRAORDINARILY COMPREHENSIVE AND HIGH EXPECTATIONS ON THE PART OF NIH TO THOSE WHO ARE RECEIVING FUNDING ABOUT THIS AREA WHICH WE ALL AGREE IS EXTREMELY IMPORTANT. AND THERE'S SIX COMPONENTS TO THE REQUIREMENTS NOW.

IT'S NOT GOOD ENOUGH TO JUST SAY I'M GOING TO SHARE IT ONCE I -- LIKE IT WILL BE SHARED IN A PUBLICATION. SO I THINK WE CAN LOOK AT THAT AND SEE HOW WE CAN PIGGYBACK RIGHT ONTO THAT, WHICH WOULD SAVE TIME.

DR. CANET-AVILES: ACTUALLY, DR. LEVITT, WE'VE ACTUALLY -- WE PRECEDED THE NIH IN THAT WE HAVE BEEN IMPLEMENTING THE DATA SHARING AND MANAGEMENT PLANS. THE NIH IS A MUCH LARGER ORGANIZATION. SO WHAT WE HAVE DONE IS WE LOOKED AT THEIR ELEMENTS, AND WE IMPLEMENTED THAT, WE'VE REVISED IT. WE HAVE DATA ADVISORS, AND WE HAVE BEEN WORKING VERY CLOSELY WITH THOSE ADVISORS AND CONSULTANTS IN THE IMPLEMENTATION OF THIS IN OUR DISCOVERY PROGRAMS. SO THAT COULD BE FEEDING INTO THE NEXT PHASE. IT'S ALWAYS STAGED. SO IF WE HAVE THIS MULTIDISCIPLINARY NEURODISCOVERY CONCEPT, THAT COULD BE THEN IMPLEMENTING THOSE DATA SHARING AND MANAGEMENT PLANS THAT WE HAVE.

GREAT POINT. AND THANK YOU FOR BRINGING

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IT UP BECAUSE IT HIGHLIGHTS HOW CIRM STAFF HAS BEEN WORKING VERY HARD ON THIS. THANK YOU.

DR. LEVITT: THAT'S GREAT. THANK YOU.

CHAIRMAN GOLDSTEIN: GREAT. ANY OTHER QUESTIONS BEFORE WE GO TO DRS. NEALE AND SEBAT? WE'LL HAVE PLENTY OF TIME FOR DISCUSSION AT THE END, I HOPE, AS WELL. SEEING NOTHING, LET ME GIVE A QUICK INTRO TO BOTH SPEAKERS.

DR. NEALE IS CO-DIRECTOR OF THE PROGRAM IN MEDICAL AND POPULATION GENETICS AT THE BROAD INSTITUTE. HE'S ALSO DIRECTOR OF GENETICS AT THE STANLEY CENTER FOR PSYCHIATRIC RESEARCH. HE'S AN ASSOCIATE PROFESSOR IN THE ANALYTIC AND TRANSLATIONAL GENETICS UNIT AT MASS GENERAL WHERE HE DIRECTS THE GENOMICS OF PUBLIC HEALTH INITIATIVE. HE'S ALSO AN ASSOCIATE PROCESSOR OF MEDICINE AT HARVARD MEDICAL SCHOOL. AND HE'S WORKING ON TRYING TO UNDERSTAND THE GENETICS OF COMMON COMPLEX HUMAN DISEASES. YOU CAN SEE HOW THIS IS DIRECTLY RELEVANT.

DR. JONATHAN SEBAT, WHO WE'LL HEAR FROM SECOND, IS THE DIRECTOR OF THE BEYSTER CENTER FOR PSYCHIATRIC GENOMICS AND PROFESSOR OF PSYCHIATRY AND CELLULAR AND MOLECULAR MEDICINE AT UC SAN DIEGO. JONATHAN'S AN EXPERT IN THE GENETIC ANALYSIS OF

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MAJOR MENTAL HEALTH DISORDERS BY DNA SEQUENCING.

SO BOTH INDIVIDUALS, AS YOU WILL SEE, ARE VERY ACCOMPLISHED IN AREAS RELATED TO THE GENETICS AND GENOMICS OF THESE VERY COMPLICATED DISEASES. AND I'LL JUST MAKE AN EDITORIAL COMMENT IN PASSING, WHICH IS IF ONE WANTS TO DEVELOP STEM CELL-BASED MODELS OF NEURONS AND GLIA THAT POTENTIALLY HAVE CHANGES LEADING TO NEUROPSYCHIATRIC DISEASE, FINDING GENES THAT ARE ALTERED IN DISEASE POPULATIONS OR FAMILIES WILL BE REALLY KEY TO BEING ABLE TO MAKE THAT STEP TECHNOLOGICALLY.

SO WITHOUT ANY MORE INTRO, LET ME TURN THE PODIUM OVER TO DR. BENJAMIN NEALE. DR. NEALE, PLEASE.

DR. NEALE: THANK YOU, DR. GOLDSTEIN. I'VE GOT A FEW SLIDES TO SHARE. I'LL BE TALKING ABOUT A NUMBER OF PIECES OF WORK AND TRY AND GIVE A BIT OF AN OVERALL VIEW AND FLAVOR OF WHAT'S GOING ON IN THE COMMUNITY MORE BROADLY.

DOWN AT THE BOTTOM ARE THE KIND OF THREE MOST RECENT PROBABLY RELEVANT CITATIONS, AND THERE ARE A FEW OTHER CITATIONS THAT I'LL TOUCH ON AS WE GO. BUT, YEAH, LET'S DIG IN TO WHERE WE ARE IN UNDERSTANDING SCHIZOPHRENIA, BIPOLAR DISORDER FROM A GENETIC ANALYSIS POINT OF VIEW.

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SO AS YOU MENTIONED, I DIRECT THE GENETICS PROGRAM AT THE STANLEY CENTER. I WON'T READ THE MISSION OF THE STANLEY CENTER, BUT I WILL JUST SAY THAT THE MISSION OF THE STANLEY CENTER IS EXTREMELY ALIGNED TO THE GOALS THAT ARE BEING ARTICULATED HERE FOR THE KIND OF NEURO-FOCUSED EFFORTS FROM CIRM. AND WE FIRMLY BELIEVE IN GENETICS AS A KIND OF POWERFUL STARTING POINT FOR BIOLOGICAL INQUIRY, PARTICULARLY WITH THE DEVELOPMENT AND EVOLUTION OF GENOMIC PROFILING TECHNOLOGIES OVER THE COURSE OF THE LAST, SAY, 10 TO 15 YEARS.

SO WHAT ARE THEY? WHAT ARE THOSE TECHNOLOGIES THAT REALLY LIVE UNDERNEATH THE STUDIES THAT I'M GOING TO DESCRIBE? THERE ARE MAINLY, I WOULD SAY, THREE PARADIGMS BEING PURSUED IN THE GENETIC ANALYSIS OF ANY DISEASE, BUT PARTICULARLY FOR SCHIZOPHRENIA AND BIPOLAR DISORDER. THERE ARE GENOTYPING ARRAYS ON THE LEFT-HAND SIDE, EXOME SEQUENCING AND GENOME SEQUENCING IN THE MIDDLE. AND THEN ON THE RIGHT-HAND SIDE, THE GENOTYPING ARRAYS ARE FOCUSED ON COMMON GENETIC VARIATIONS.

SO MOST DIFFERENCES BETWEEN MOST PEOPLE ARE COMMON GENETIC VARIANTS RATHER THAN RARE GENETIC VARIANTS. AND LARGE-SCALE INTERNATIONAL COLLABORATIVE EFFORTS TO COLLECT THE COMMON GENETIC

VARIATION ACROSS THE HUMAN SPECIES HAVE BEEN BROADLY SUCCESSFUL. A LOT OF THEM WERE LAUNCHED RIGHT AFTER THE COMPLETION OF THE HUMAN GENOME PROJECT. SO IT WAS SORT OF SEQUENCE A GENOME AND THEN GO ABOUT TRYING TO COLLECT COMMON GENETIC VARIATION ACROSS THE GENOME. THAT THEN GETS PUT ONTO GENOTYPING ARRAYS. AND THEY WORK TO REALLY CAPTURE PRIMARILY THINGS THAT ARE, SAY, 1 PERCENT OR SO ARE MORE COMMON IN THE KIND OF VARIOUS HUMAN GENETIC ANCESTRIES THAT ARE OUT THERE IN THE BIG, WIDE WORLD.

GWAS HAS BEEN A MAINSTAY OF GENETIC ANALYSIS FOR SCHIZOPHRENIA, FOR BIPOLAR DISORDER, FOR, I SUPPOSE, AT LEAST THE LAST, I GUESS, DECADE. AND I'LL GO INTO WHAT WE ARE LEARNING A LITTLE BIT THERE AND SOME OF THE CHALLENGES INHERENT WITH INTERPRETING THOSE FINDINGS.

MORE RECENTLY, AFTER SEQUENCING ONE HUMAN GENOME AT THE COST OF MANY BILLIONS OF DOLLARS, IT'S NOW POSSIBLE TO SEQUENCE THE HUMAN GENOME EITHER FOCUSING JUST ON THE PROTEIN CODING REGIONS AT A KIND OF SLIGHTLY CHEAPER COST, BUT ON THE ORDER OF HUNDREDS OF DOLLARS RATHER THAN THE BILLIONS OF DOLLARS IT WAS WHEN WE STARTED OR GOING UP TO A KIND OF DEEPER GENOME, WHICH IS MORE EXPENSIVE THAN THE

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EXOME SEQUENCING, BUT ALLOWS COMPLETE COMPREHENSIVE CAPTURE OF GENETIC VARIATION MORE BROADLY.

NOW, TO ME, IN THE CONTEXT OF STEM CELL RESEARCH AND WHAT WE ARE DOING IN THESE MODEL SYSTEMS, THERE'S VALUE IN SEQUENCING NOT JUST ONCE, BUT THERE'S SOME VERY NICE WORK FROM STEVE MCCARROL AND KEVIN EGGAN ABOUT CLONAL EXPANSIONS OCCURRING IN IPS-DERIVED MODELS. AND SO SORT OF SEQUENCING IS A SORT OF OVERALL GENOMIC HEALTH OF THE MODEL SYSTEM, AND THE STEM CELL CIRCUMSTANCE IS SOMETHING ELSE THAT'S ACTUALLY QUITE VALUABLE ABOVE AND BEYOND OUR ATTEMPTS TO, LIKE, UNDERSTAND DISEASE MECHANISM, WHICH I WILL SPEND MOST OF THE REST OF THE TALK TALKING ABOUT.

OKAY. SO THE STANLEY CENTER HAS BEEN DEEPLY COMMITTED AND INTEGRATED WITH TRYING TO UNDERSTAND THE GENETIC BASIS OF NEUROPSYCHIATRIC DISORDERS, PARTICULARLY SCHIZOPHRENIA AND BIPOLAR DISORDER, SINCE ITS FOUNDING. AND HERE'S KIND OF A FEW FIGURES FROM OUR LATEST PUBLICATION CALLED "THE SCHIZOPHRENIA EXOME META-ANALYSIS INITIATIVE."

ON THE LEFT-HAND SIDE YOU SEE THIS SORT OF CASE CONTROL DESIGN AND THE NUMBER OF INDIVIDUALS. IT'S ABOUT 25,000 INDIVIDUALS WITH SCHIZOPHRENIA RECRUITED ACROSS MANY DIFFERENT PLACES IN THE WORLD,

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ALTHOUGH THE VAST MAJORITY OF THE COHORTS AT THIS POINT IN TIME ARE COMING FROM THE U.S. AND EUROPE. THERE ARE A FEW OTHER COLLECTIONS IN SOME EAST ASIAN POPULATIONS, BUT, BROADLY SPEAKING, THIS IS LARGELY EUROPEAN GENETIC ANCESTRY.

I WILL PAUSE AND SAY THAT GENETIC ANCESTRY IS NOT THE SAME AS RACE OR ETHNICITY, AND WE SHOULD BE ACTUALLY VERY EXPLICIT ABOUT THAT DISTINCTION. THE RIGHT-HAND SIDE OF THIS PICTURE IS A SORT OF REPRESENTATION OF COMMON GENETIC VARIATION AND SHOWS GENETIC SIMILARITY TO A FIRST APPROXIMATION ACROSS INDIVIDUALS REPRESENTED ACROSS THE COHORT. BUT THE GENERAL IDEA HERE IS THAT WE GO OUT AND FIND PEOPLE WITH SCHIZOPHRENIA, COLLECT SAMPLES, PROFILE THEIR DNA, AND THEN COMPARE THAT TO INDIVIDUALS THAT DON'T HAVE SCHIZOPHRENIA, OR GIVEN HOW RARE SCHIZOPHRENIA IS AS AN OUTCOME, SOMEWHERE BETWEEN HALF A PERCENT AND 1 PERCENT. MORE GENERALLY, YOU CAN JUST SORT OF COMPARE THEM AGAINST RANDOM INDIVIDUALS FROM SIMILAR GENETIC ANCESTRY IS THE BEST ADVICE FROM A KIND OF GENIC ANALYSIS POINT OF VIEW.

AND FOR EXOME SEQUENCING, WE ARE FOCUSING IN JUST ON GENES AND JUST ON CODING VARIATIONS SINCE THEY OFFER BOTH THE FASTEST INTERPRETATION FOR GENETIC SIGNALS, BUT ALSO HAVE EMPIRICALLY SHOWN TO

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HAVE THE LARGEST EFFECT SIZES THUS FAR FOR PRETTY MUCH ANY CLASS OF GENETIC VARIATION THAT WE'VE STUDIED.

WE ALSO HAVE A SET OF TRIOS. SO PARENTS AND THEN A CHILD WITH SCHIZOPHRENIA AND RECRUITED ALL THREE MEMBERS OF THE PEDIGREE AND THEN LOOK, NOT ONLY FOR VARIATION THAT'S TRANSMITTED FROM PARENT TO OFFSPRING, BUT ALSO NEWLY ARISING OR DE NOVO MUTATIONS WHICH CAN HAVE AN EVEN GREATER IMPACT SINCE THAT'S A CLASS OF VARIATION THAT OCCURS AT A VERY LOW BASE RATE AND THE FORCES OF NATURAL SELECTION HAVE NOT HAD AN OPPORTUNITY TO NECESSARILY ACT ON THAT CLASS OF VARIATION AT THIS POINT IN TIME.

SO TAKING OVERALL A KIND OF GENERAL VIEW OF WHAT WE ARE SEEING FROM SCHEMA, THERE'S THIS ENRICHMENT OF SORT OF RARE PROTEIN-TRUNCATING VARIANTS, THINGS THAT KNOCK OUT ONE OF THE TWO COPIES OF EACH GENE IN THE HUMAN GENOME THAT YOU CARRY. THESE RARE PROTEIN-TRUNCATING VARIANTS, IN GENES WHERE SURVEYS OF HUMAN GENETIC VARIATION MUCH MORE BROADLY ACROSS HUNDREDS OF THOUSANDS OF INDIVIDUALS, THESE GENES ARE PARTICULARLY DEVOID OF THOSE MUTATIONS IN HUMANS LIKELY BECAUSE NATURAL SELECTION HAS LED TO THE REDUCTION IN THE FREQUENCY

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OF THESE GENE KNOCKOUTS. AND IF WE FOCUS JUST ON THESE GENES THAT ARE UNDER STRONG, PURIFYING NATURAL SELECTION, WE SEE AN INCREASED RATE OF THIS CLASS OF PROTEIN-TRUNCATING VARIANTS.

SO THESE STRONG ACTING MUTATIONS THAT ARE KNOCKING OUT ONE OF THE TWO COPIES OF THE GENE ARE CLEARLY ENRICHED IN INDIVIDUALS WITH SCHIZOPHRENIA COMPARED TO INDIVIDUALS WITHOUT SCHIZOPHRENIA. AND NOT ONLY DO WE SEE AN ENRICHMENT OVERALL IN THIS CLASS OF VARIATION, WE HAVE HERE ON THE RIGHT A QQ PLOT, WHICH IS JUST A WAY OF SHOWING THE FULL DISTRIBUTION OF ASSOCIATION RESULTS FROM THE ANALYSIS. AND YOU CAN SEE THAT THERE ARE KIND OF NOW TEN GENES THAT HAVE SURPASSED THE THRESHOLD FOR EXOMEWIDE SIGNIFICANCE WHERE WE ARE QUITE CONFIDENT THAT THEY HAVE A VERY LARGE IMPACT ON SCHIZOPHRENIA RISK MORE GENERALLY. AND I'LL GO A LITTLE BIT FURTHER INTO SOME OF THE THINGS THAT WE ARE LEARNING AS WE CONTINUE THROUGH.

IN ADDITION TO PROBING RARE VARIATION THROUGH THAT SEQUENCING APPROACH, PRIMARILY EXOME SEQUENCING, WE ARE ALSO PURSUING COMMON VARIANT DISCOVERY IN COLLABORATION WITH THE PSYCHIATRIC GENOMICS CONSORTIUM. THIS IS, AGAIN, SAME SORT OF APPROACH: COLLECT PEOPLE WITH SCHIZOPHRENIA,

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COLLECT PEOPLE WITHOUT SCHIZOPHRENIA, TAKE SAMPLES FOR THEM, AND NOW HERE LOOK AT COMMON GENETIC VARIANTS USING THOSE GENOTYPING ARRAYS.

AND WHAT WE'VE FOUND FROM THIS KIND OF SURVEY OF COMMON GENETIC VARIATION IS THAT COMMON GENETIC VARIANTS MATTER AS PART OF THE RISK FACTORS. FOR SCHIZOPHRENIA, INDEED, THEY REPRESENT THE LARGEST FRACTION OF ATTRIBUTABLE GENETIC RISK THAT WE CAN IDENTIFY WHEN PURSUING OUR INTERPRETATION OF EITHER BE IT SCHIZOPHRENIA OR BIPOLAR DISORDER, BUT MOST OF THESE EFFECT SIZES ARE MARKEDLY MUCH SMALLER THAN THE KIND OF RARE VARIANTS OF STRONG EFFECT THAT ARE BEING IDENTIFIED FROM SCHEMA.

NOW, A NATURAL QUESTION TO ASK WHEN YOU'RE TRYING TO KIND OF TRAVERSE DIFFERENT ASPECTS OF GENETIC RISK IS WHETHER OR NOT THERE ARE CONVERGING SIGNALS COMING FROM THE COMMON VARIANT SCANS AND WHAT WE SEE ON THE RARE VARIANT SCANS. AND THE ANSWER TO THAT IS, AT LEAST AT A FIRST APPROXIMATION, YES, WE ARE SEEING CONVERGENCE. SO IT'S DIFFICULT TO INTERPRET EXACTLY WHAT THE MECHANISM OF A COMMON VARIANT ASSOCIATION IS. MOST COMMON VARIANT ASSOCIATIONS ARE NONCODING. FIGURING OUT HOW A NONCODING, SO A GENETIC VARIANT THAT LIES OUTSIDE OF THE PROTEIN CODING REGION, WHAT IT'S

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ACTUALLY DOING IS A VERY CHALLENGING THING TO DO, BUT WE HAVE A VARIETY OF DIFFERENT APPROACHES THAT WE APPLY TO TRY AND PRIORITIZE GENES FROM THESE KINDS OF ANALYSES. YOU CAN READ ABOUT THIS MORE DEEPLY IN THE PDC SCHIZOPHRENIA PAPER.

BUT WHEN WE TAKE GENES PRIORITIZED FROM COMMON VARIANT ANALYSES AND THEN GO AND ASK THE QUESTION IN THE RARE VARIANT CODING -- RARE CODING VARIANT ANALYSIS, IS THIS A KIND OF SET OF GENES THAT ARE ENRICHED FROM MUTATIONS THAT WE MIGHT THINK HAVE AN OUTSIDE BIOLOGICAL IMPACT IN INDIVIDUALS WITH SCHIZOPHRENIA COMPARED TO INDIVIDUALS THAT DON'T HAVE SCHIZOPHRENIA? THE ANSWER TO THAT IS VERY CLEARLY YES.

AND THEN NOT ONLY ARE THE TEN GENES EXCITING, BUT THERE'S VERY CLEAR EVIDENCE THAT THERE IS A KIND OF CONTINUED BULK OF RARE VARIANT SIGNAL THAT REMAINS TO BE DISCOVERED IF AND WHEN WE INCREASE THE SAMPLE SIZES FOR PRIMARY GENETIC DISCOVERY IN SEQUENCING.

SO HERE'S A PICTURE OF THE OVERALL LANDSCAPE OF THE GENETIC ARCHITECTURE OF SCHIZOPHRENIA THAT WE KNOW RIGHT NOW. THIS IS BASICALLY EVERYTHING WE KNOW ABOUT SCHIZOPHRENIA GENETICS AT THIS POINT. AND YOU CAN SEE THAT THE

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RED DOTS -- THESE ARE THOSE KIND OF CODING VARIANT GENE DISCOVERIES THAT I WAS MENTIONING A BIT EARLIER -- THEY HAVE ODDS RATIOS RANGING FROM 3, 4, 5 UP TO 10, 20, MAYBE EVEN 50.

THE GREEN DOTS ARE COPY NUMBER VARIANTS, LARGE CHROMOSOMAL DELETIONS OR DILUTION, LARGE CHUNKS OF CHROMOSOMES THAT ARE DELETED OR DUPLICATED, OR IN SOME INSTANCES A VERY SPECIFIC GENE THAT GETS DELETED OR KIND OF INTERFERED WITH FROM A STRUCTURAL VARIANT POINT OF VIEW QUITE FREQUENTLY LIKE THE NKRN1 DELETION THAT YOU CAN SEE.

AND THESE GREEN DOTS HAVE EVEN BIGGER EFFECT SIZES AND MAYBE EVEN STRONGER ODDS RATIOS, BUT ARE MUCH MORE COMPLICATED TO INTERPRET BECAUSE MOST OF THESE REGIONAL -- MOST OF THESE COPY NUMBER VARIANTS ARE LARGE SEGMENTS THAT ENCOMPASS MANY GENES AND ARE MUCH MORE COMPLICATED TO FIGURE OUT.

ON THE RIGHT-HAND SIDE IN THE BLUE DOTS, THESE ARE THE COMMON VARIANTS THAT ARE COMING OUT OF THE GWAS. AND I'VE POINTED OUT A COUPLE THAT MAYBE HAVE BEEN FINE MAPPED TO EITHER A CODING VARIANT, AS IS THE CASE IN SLC39A8, OR ACTUALLY A GENE DUPLICATION EVENT THAT IS THE C4 KIND OF CALL-OUT FOR THE KIND OF POTENTIAL GENE THERE. BUT YOU CAN SEE THAT THE EFFECT SIZES ARE MUCH MORE LIKE ODDS

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RATIOS OF 1.05, MAYBE 1.1, MAYBE 1.2 IN THE VERY KIND OF OUTSIDE.

SO THESE ARE SUBTLE NUDGES ON RISK, BUT THERE ARE A GREAT MANY OF THEM. THAT'S THE KIND OF COMMON POLYGENIC COMPONENT. AND THEN THERE ARE THESE RARE VARIANTS OF LARGE EFFECT THAT HAVE A MUCH MORE MARKED IMPACT ON AN INDIVIDUAL'S RISK, BUT ARE CONSIDERABLY RARER IN THE POPULATION. YOU CAN SEE THE MINOR ALLELE FREQUENCY HERE ON THE X AXIS.

SAME KIND OF STORY FOR BIPOLAR DISORDER IS THE MOST RECENT BIPOLAR DISORDER PUBLISHED GWAS. AGAIN, COMPLICATED POLYGENIC INHERITANCE, CONVERGING RISK FACTORS WITH WHAT WE INVESTIGATE IN SCHIZOPHRENIA. SO THERE'S SOME OVERLAP IN THE GENETIC RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER MORE GENERALLY.

INCREASING SAMPLE SIZES TO FIND MORE ASSOCIATIONS, WE AT THE BROAD HAVE PURSUED A BIPOLAR EXOME SEQUENCING STUDY THAT WE'VE DONE ON ABOUT 17,000 INDIVIDUALS WITH BIPOLAR AND A SIMILAR NUMBER OF MATCH CONTROLS TO A FIRST APPROXIMATION. ALMOST ALL OF THESE COHORTS ARE DRAWN FROM THE U.S. OR EUROPE WITH PRETTY LIMITED REPRESENTATION IN TERMS OF THE KIND OF GENETIC ANCESTRY AND ETHNICITY AND RACE QUESTIONS.

BUT IMPORTANTLY, OUR KIND OF, AGAIN, QQ PLOT, OVERALL DISTRIBUTION OF THE ASSOCIATION ANALYSIS, TESTING EVERY SINGLE GENE IN THE GENOME FOR AN ENRICHMENT OF LOSS-OF-FUNCTION MUTATIONS OR MISSENSE MUTATIONS AGAINST INDIVIDUALS WITHOUT THE DISORDER, YOU SEE THIS TOP HIT HERE IS THIS GENE AKAP11. SO AKAP11 KIND OF POPS UP NEAR THE TOP FOR BOTH SCHIZOPHRENIA AND BIPOLAR DISORDER. IT'S GOT A COMBINED P-VALUE OF AROUND 10 TO THE MINUS 9 IF YOU TRAVERSE THE SCHIZOPHRENIA AND BIPOLAR DISORDER LANDSCAPE.

PART OF THE REASON THAT WE ARE VERY INTERESTED IN THE AKAP11 LOSS-OF-FUNCTION MUTATIONS IS THAT THERE ARE NO DE NOVO LOSS-OF-FUNCTION MUTATIONS OBSERVED IN THE DECIPHERING DEVELOPMENTAL DELAY PROGRAM THAT HAS BEEN LAUNCHED OUT OF THE SANGER INSTITUTE IN THE UK. AND SO IT REALLY DOES SEEM TO BE A LITTLE BIT MORE SPECIFIC TO THE SCHIZOPHRENIA AND BIPOLAR END OF THE NEUROPSYCHIATRIC DISORDER LANDSCAPE COMPARED TO SOME OF THE OTHER DISCOVERIES THAT DO SHOW OVERLAP, BUT PERHAPS WITH INTELLECTUAL DISABILITY OR OTHER FORMS OF SEVERE NEURODEVELOPMENTAL PROBLEMS.

BUT PART OF THE REASON WE ARE SO EXCITED ABOUT AKAP11 IS WHAT IT'S KNOWN TO BE DOING IN

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HUMANS. AND SO THERE'S THIS LOVELY PAPER FROM THE *JOURNAL OF BIOLOGICAL CHEMISTRY* THAT SHOWS THAT AKAP11 MAKES THIS PROTEIN AKAP 220. AKAP 220 BINDS WITH GSK3ß, AND IT IS LIKELY INVOLVED IN THE PHOSPHORYLATION OF GSK3ß BY A PROTEIN CALLED PKA OR PROTEIN KINASE A-DEPENDENT INHIBITION OF GSK3ß. AND THAT'S EXCITING BECAUSE LITHIUM THERAPY IS THOUGHT TO INHIBIT GSK3 MORE GENERALLY AMONG OTHER THINGS AND DOES TREAT A SUBSET OF INDIVIDUALS WITH BIPOLAR DISORDER.

SO HERE WE ARE SEEING SOMETHING THAT'S GOT AT LEAST AN INITIAL INDICATION, SOME CLEAR, STRONG ACTING GENETIC RISK CONFERRED TO SCHIZOPHRENIA AND BIPOLAR DISORDER AND SOME CLUES THAT MIGHT POINT TO POTENTIAL MECHANISTIC FOLLOW-UP STUDIES ABOUT THE RELATIONSHIP BETWEEN KNOCK DOWN OF AKAP11 AND WHAT THAT MIGHT DO TO GSK3ß THAT ALSO INTERFACES WITH KNOWN PHARMACOLOGICAL AGENTS THAT HAVE AN IMPACT ON THESE ILLNESSES.

NOW, I'LL JUST CLOSE WITH A FEW NEAR-TERM PLANS BECAUSE I UNDERSTAND THAT THERE ARE LOTS OF DIFFERENT GOALS IN THE CONTEXT OF THE CIRM EFFORT HERE AND WHAT THE NEURO TASK FORCE IS CONCERNING ITSELF WITH. AND SO I THOUGHT I'D DESCRIBE FOR YOU THE MARKEY SEQUENCING PROGRAM THAT WE HAVE FUNDED IN

PARTNERSHIP BY NIMH WITH SUPPORT FROM THE STANLEY CENTER AND MANY, MANY OTHERS CALLED THE "POPULATIONS UNDERREPRESENTED IN MENTAL ILLNESS ASSOCIATION STUDIES."

AND HERE WHAT WE'VE DONE IS BUILT A SAMPLE COHORT OF 120,000 INDIVIDUALS, INCLUDING RECRUITMENT SITES FROM UGANDA, ETHIOPIA, KENYA SOUTH AFRICA, BUT ALSO COLOMBIA, BRAZIL, ACROSS THE AMERICAS IN NEW YORK AND IN SOUTHERN CALIFORNIA, ALL FOCUSED RECRUITMENT ON INDIVIDUALS WITH EITHER, IN THE U.S. CONTEXT, AFRICAN-AMERICANS OR HISPANIC LATINOS, AND IN THE MORE GLOBAL CONTEXT OF COHORTS AND GENETIC ANCESTRIES GROSSLY UNDERREPRESENTED IN THE GENETIC STUDIES THAT WE'VE DONE HERETOFORE.

WE ARE FUNDED FOR THIS. WE HAVE KIND OF SAMPLES IN PLACE. AND OVER THE COURSE OF THE NEXT, SAY, TWO TO THREE YEARS, WE SHOULD BE DELIVERING THIS OVERALL DATASET WITH CONTINUED GENETIC INVESTIGATION, NOT ONLY HOPEFULLY REINFORCING THE GENETIC DISCOVERIES THAT WE'VE MADE THUS FAR, BUT IDENTIFYING ADDITIONAL GENES IN THAT KIND OF UNKNOWN, UNTAPPED BURDEN PARTS THAT I SHOWED YOU A LITTLE BIT EARLIER. AND SO THIS WILL ALMOST ASSUREDLY DELIVER ADDITIONAL GENETIC INSIGHTS AND BE PERHAPS MUCH MORE BROADLY REPRESENTATIVE OF THE

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CALIFORNIAN POPULATION THAN THINGS THAT WE'VE DONE THUS FAR.

AND THIS FITS INTO THIS KIND OF EMERGING PARADIGM THAT WE ARE ALL STRUGGLING WITH IN HUMAN GENETICS. LIKE THIS IS NOT JUST SPECIFIC TO NEUROPSYCHIATRIC DISEASE, BUT IS HOW DO WE TRAVERSE THE SPACE FROM GENETIC DISCOVERY INTO INSIGHTS INTO WHAT GENES MATTER, WHAT CELL TYPES MATTER, WHAT BIOLOGICAL PROCESSES MATTER, AND HOW DOES THAT GIVE RISE TO INSIGHTS INTO DISEASE MECHANISM AND THERAPEUTIC HYPOTHESES.

GENETIC DISCOVERY IS ABSOLUTELY WORKING. THE CHALLENGE NOW IS TO TAKE THESE GENETIC DISCOVERIES AND PUT THEM IN MODEL SYSTEMS TO PROBE WHAT THE BIOLOGICAL CONSEQUENCES OF THESE GENETIC PERTURBATIONS ARE. WHAT WOULD AN AKAP11 KNOCKOUT DO IN A NEURONAL MODEL SYSTEM? HOW IS THAT SHAPING THE ELECTROPHYSIOLOGICAL READOUTS OF NEURONS, ET CETERA, ET CETERA, ET CETERA? THOSE ARE THE KIND OF QUESTIONS THAT WE WILL NEED TO TURN TO IN THE COMING YEARS TO TRY AND DEEPEN OUR UNDERSTANDING OF WHAT THESE GENETIC RISK FACTORS ARE ACTUALLY DOING BIOLOGICALLY.

AND WITH THAT, I WILL CLOSE. I THINK I TOOK MY 20 MINUTES AND OPEN THE FLOOR FOR QUESTIONS

IF NOW IS THE RIGHT TIME.

CHAIRMAN GOLDSTEIN: THANK YOU VERY MUCH, DR. NEALE. QUITE AN EXCITING PRESENTATION. QUESTIONS FROM THE GROUP? J.T.

CHAIRMAN THOMAS: THANK YOU, DR. NEALE, VERY MUCH FOR THAT ELEGANT PRESENTATION.

OBVIOUSLY THIS IS EARLY DAYS IN ALL OF THIS, BUT NOW THAT YOU'VE IDENTIFIED SOME POTENTIAL GENE TARGETS, HOW LONG WOULD YOU ANTICIPATE, GIVEN THE ORDINARY COURSE OF THINGS, THAT IT WILL TAKE TO GET TO A POINT WHERE YOU HAVE SOME THERAPEUTIC CANDIDATES FOR EITHER OF THESE CONDITIONS?

DR. NEALE: IT'S DIFFICULT QUESTION. I MEAN THERE'S THE -- SO THERE'S SORT OF TWO ROADS THAT YOU CAN THINK ABOUT WALKING DOWN. I THINK THE FIRST AND MOST IMPORTANT QUESTION IS WHAT OF THIS -- WHAT IS THE ACTUAL MECHANISM BY WHICH THE DISEASE PATHOGENESIS IS ARISING? AND THAT MEANS YOU NEED TO HAVE KIND OF CLARITY ON WHY KNOCKING OUT THIS GENE OR PERTURBING THIS GENE IN THIS CONTEXT IS HAVING THE ACTUAL DISEASE MECHANISTIC CONSEQUENCE. THAT MEANS WORKING THE BASIC BIOLOGY. IT MEANS UNDERSTANDING THE BIOCHEMISTRY. IT MEANS MAYBE EVEN IDENTIFYING BIOMARKERS FOR THOSE KINDS OF BIOLOGICAL PERTURBATIONS.

JUDGING ON OTHER SUCH ARCS IN OTHER PARTS OF MEDICINE, I'D SAY IT'S SOMETHING LIKE A 15- TO 20-YEAR JOURNEY FROM THIS KIND OF DISCOVERY TO APPROVED MEDICATION, MAYBE EVEN A LITTLE BIT LONGER IF YOU THINK ABOUT, SAY, PCSK9 INHIBITORS NOW AS AN APPROVED MEDICATION. THOSE INITIAL GENETIC DISCOVERIES WERE 20 PLUS YEARS AGO. SO THAT'S THE SORT OF TIME FRAME.

NOW, NATURALLY WE ARE MEANT TO BE BETTER AND SMARTER AT THESE SORTS OF THINGS. OUR MODELS ARE MORE SOPHISTICATED. THEY'RE MEANT TO BE A LITTLE BIT MORE RAPID. SO THAT'S ONE POSSIBILITY.

THE OTHER SIDE OF THE EQUATION MAYBE IS THAT, LIKE WITH INNOVATIONS AND THINGS LIKE GENE EDITING OR BASE EDITING OR CRISPR, THAT THERE MAY BE OTHER WAYS OF MORE DIRECTLY TARGETING THOSE MUTATIONS THEMSELVES IN THE FRACTION OF PATIENTS THAT CARRY SUCH MUTATIONS.

I DIDN'T SAY THIS THAT EXPLICITLY, BUT THE CARRIER RATE FOR MOST OF THESE MUTATIONS IN INDIVIDUALS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER IS ABOUT ONE IN A THOUSAND. SO THAT'S LIKE ALSO A VERY COMPLICATED ROAD TO GO DOWN; BUT IF YOU RESTORE THE FUNCTION OF THAT GENE IN BOTH ITS COPIES, MAYBE THAT HELPS. IT'S A BIT MORE SPECULATIVE, AND

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THERE'S PROBABLY HIGHER RISK ASSOCIATED WITH PURSUING THAT PARTICULAR THERAPEUTIC STRATEGY, BUT IT IS A LEGITIMATE ALTERNATE APPROACH TO TRYING TO FINESSE OUT WHAT EXACTLY THE DISEASE MECHANISM IS EXPLICITLY.

CHAIRMAN GOLDSTEIN: OKAY. I'M GOING TO CALL ON MYSELF AND THEN I'LL CALL ON PAT.

A COUPLE QUICK QUESTIONS. SO IN NEURODEGENERATIVE DISORDERS, WHICH I'VE WORKED ON IN THE PAST, ONE COMMON OBSERVATION IS THAT, AS I UNDERSTAND IT, VIRTUALLY EVERY NEURODEGENERATIVE DISORDER, WHEN EXAMINED POST MORTEM SHOWS SIGNIFICANT EVIDENCE OF NEUROINFLAMMATION. AND IT APPEARS TO BE A REALLY IMPORTANT PART OF DRIVING SOME OF THESE DISORDERS.

ARE THERE ANALOGOUS POST MORTEM DATA IN ANY OF THESE WHAT WE'LL CALL PSYCHIATRIC DISORDERS? ANYWAY, YOU GET MY DRIFT.

DR. NEALE: YEAH. I GOT THE DRIFT. SO NEUROPATHOLOGISTS HAVE BEEN TRYING TO EXPLORE OBVIOUS PATHOLOGICAL DIFFERENCES IN THE CONTEXT OF SCHIZOPHRENIA AND BIPOLAR COMPARED TO INDIVIDUALS WITHOUT AND I THINK IN QUITE, I THINK, MARKED CONTRAST WITH NEURODEGENERATIVE DISORDER HAS NOT REALLY DELIVERED MUCH IN THE WAY OF OBVIOUS BE IT

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STRUCTURAL OR EVEN CELLULAR READOUTS THAT ARE CLEARLY ASSOCIATING WITH THESE OUTCOMES. I WILL SAY THAT A LOT OF THE GENETIC EVIDENCE DOES POINT TO THE SYNAPSE AND SYNAPTIC FUNCTION, AND IT MAY BE THAT THE GRANULARITY OF NEUROPATHOLOGY IS INSUFFICIENTLY DETAILED AT THIS JUNCTION TO GET CLARITY ON THE DEGRADATION OF SYNAPTIC FUNCTION IN THIS KIND OF CONTEXT. BUT EVEN THEN I'M SORT OF SPECULATING ABOUT EXACTLY WHAT THE MECHANISM IS BECAUSE, WHILE THE GENETICS SUPPORTS SYNAPSE, IT DOESN'T CONCLUSIVELY TELL US THAT THAT IS WHERE THE PROBLEMS LIE.

STEVE MCCARROLL AND EVAN MACOSKO, COLLEAGUES HERE AT THE STANLEY CENTER, THAT DEVELOPED A LOT OF THE SINGLE-CELL TRANSCRIPTOMIC PROFILING ACTIVITIES HAVE ALSO PURSUED SIMILAR KINDS OF INVESTIGATIONS. AND I DON'T THINK THAT THERE'S ANYTHING OVERWHELMING EMERGING AT THIS POINT IN TIME THAT WOULD POINT TO AN OBVIOUS NEUROPATHOLOGY AS THE SOURCE OF THESE PARTICULAR ILLNESSES.

CHAIRMAN GOLDSTEIN: OKAY. VERY GOOD. THANK YOU. AND THEN A SECOND QUESTION BEFORE WE GO TO PAT. SORRY, PAT.

THE IDENTIFICATION OF KINASES, YET AGAIN IN ONE OF THESE NEUROPSYCHIATRIC DISORDERS, IS

REALLY STRIKING. AND, OF COURSE, THAT ALSO OVERLAPS WITH SOME OF THE DEGENERATIVE DISORDERS. I GUESS THE QUESTION IS WHETHER THERE'S ANY EVIDENCE IN SOME OF THESE NEURODEGENERATIVE DISORDERS THAT THEY OVERLAP GENETICALLY AMONG THOSE CASES WHERE, SAY, PSYCHOSIS IS PART OF THE ETIOLOGY OF THE DISEASE VERSUS STRAIGHT DEGENERATION TO THE EXTENT THAT ANYTHING IS THAT SIMPLE?

DR. NEALE: YEAH. IT'S A GOOD QUESTION. I MEAN OBVIOUSLY YOU GET PSYCHOTIC FEATURES IN A VARIETY OF NEURODEGENERATIVE DISORDERS. AND INDEED ANTIPSYCHOTICS ARE USED TO TREAT THOSE SYMPTOMS AND ASPECTS OF THOSE ILLNESSES. I THINK THERE'S NOT A LOT OF SUPPORT THAT THE GENETIC INSULTS ARE SHARED UPSTREAM. AND THE TIME COURSE PRESENTATION OF THESE PARTICULAR SYMPTOMS MAYBE SUGGESTS THAT IT'S COMING THROUGH A DIFFERENT ROUTE BECAUSE SCHIZOPHRENIA AND BIPOLAR DISORDER, TYPICAL AGES OF ONSET, THERE'S THE PRODROMAL PERIOD WHERE YOU'RE MAYBE TALKING LIKE LATE ADOLESCENCE, EARLY ADULTHOOD, AND THEN FRANK PSYCHOSIS PRESENTING IN EARLY-ISH ADULTHOOD WITH DIAGNOSIS OF SOMETIMES EVEN LAGGING 5, 10, 15 YEARS AFTER INITIAL PRESENTATION OF SYMPTOMS. AND THAT'S JUST 40 OR 50 YEARS AWAY FROM NEURODEGENERATIVE DISEASES ARE GOING TO BE PRESENTING THEIR BUSINESS.

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AND SO WHILE WE MAY END UP WITH THE SAME BREAKDOWN IN SYNAPTIC FUNCTION OR SOME OF THE ALTERATIONS OF SYNAPTIC FUNCTION THAT ARE BEING INDUCED FROM THE ANTIPSYCHOTIC MEDICATION MAY EVEN HELP DEAL WITH PSYCHOTIC SYMPTOMS ON BOTH SIDES OF THE SORT OF NEURODEGENERATIVE, NEUROPSYCHIATRIC FENCE. IT DOES SEEM, AT LEAST AT THIS POINT, FROM A GENETICS POINT OF VIEW, THAT THERE'S ACTUALLY QUITE A HIGH DEGREE OF DISTINCTION IN WHAT IS DRIVING THE ILLNESSES FROM EMPATHOGENIC PROCESS POINT OF VIEW.

CHAIRMAN GOLDSTEIN: OKAY. GREAT. THANK YOU. PAT.

DR. LEVITT: THANKS VERY MUCH, BEN. THAT WAS GREAT.

I WAS GOING TO PIGGYBACK ON YOUR COMMENT ABOUT GENE EDITING AND SOME OF THE MODELS THAT ARE AMENABLE TO THAT. AND ONE OF THE THINGS THAT HAS COME OUT OF SOME OF THE ORGANOID WORK, AS WELL AS SOME RECENT GENETIC REFERENCE PANEL WORK -- I WON'T CITE MY OWN PAPER THAT JUST CAME OUT WITH CHDA, BUT THERE I DID. I JUST CITED IT -- THAT THIS ISSUE AROUND BACKGROUND, GENETIC BACKGROUND, IS SO CRITICALLY IMPORTANT IN UNDERSTANDING HETEROGENEITY EVEN OF THE MECHANISM. SO WHAT'S GOING ON IN TERMS OF GENETICS AND TRYING TO IDENTIFY THE MODIFIERS

THAT MAY END UP BEING REALLY IMPORTANT FROM EVEN A DRUG TARGETING PERSPECTIVE?

DR. NEALE: THAT'S A GOOD QUESTION, PAT. I THINK THAT'S -- A LOT OF THE EFFORT ON PURSUING COMMON VARIANT SCANS IS TO GET A HANDLE ON SORT OF THE INTRAINDIVIDUAL VARIATIONS AND SUBTLE DIFFERENCES THAT MAY BE INTRODUCED ACROSS EVEN BASIC BIOCHEMICAL REACTIONS. I THINK WE ARE OFTEN TAUGHT IN BIOLOGY THAT THERE'S, LIKE, ONE PATHWAY AND THINGS WORK IN THIS WAY. AND I THINK PART OF WHAT YOU'RE ALLUDING TO IN TERMS OF THE IMPORTANCE OF GENETIC BACKGROUND IS THAT THERE ARE LOTS OF POTENTIAL WIGGLE POINTS IN LOTS OF THESE BIOCHEMICAL PATHWAYS AND PROCESSES AND FUNCTIONS THAT CELLS AND MAYBE EVEN CIRCUITRY OR OTHER PHYSIOLOGICAL PHENOMENA RELEVANT TO BRAIN FUNCTION MIGHT ALSO SHOW DIFFERENCE.

AND THAT, I THINK, IS ANOTHER REASON TO BOTH TRY AND ENSURE THAT WE ARE AS REPRESENTATIVE AS POSSIBLE IN OUR GENETIC STUDIES BECAUSE IT GIVES US THE BROADEST POSSIBLE VIEW OF GENETIC VARIATIONS IMPACT ACROSS THESE ILLNESSES AS WELL AS THE KIND OF IMPORTANT FOLLOW-UP WORK OF, ONCE WE IDENTIFY A GENETIC RISK FACTOR, WE START TO GET TO SOME INSIGHT ABOUT HOW WE MIGHT STRATIFY GROUPS OF INDIVIDUALS

WITH A DISORDER, HOW WE MIGHT PROBE WHAT BIOMARKERS ARE RELEVANT THAT WE TRY AND KNIT TOGETHER FROM GENETIC DISCOVERY INTO WHAT THOSE INTERMEDIATE PHENOTYPES ARE THAT ARE DRIVING THE PATHOGENIC PROCESS SO THAT WE CAN UNDERSTAND THAT DISEASE AT ITS KIND OF MOST FUNDAMENTAL MECHANISM. AND SO DIVERSITY IN THE LINES, DIVERSITY IN THE KIND OF STARTING CELLULAR MATERIAL IS ABSOLUTELY ESSENTIAL FROM WHERE I SIT AND SOMETHING THAT I'VE BEEN ADVOCATING HERE LOCALLY FOR QUITE A LONG TIME. AND I'M HAPPY TO DO SO FROM MY SOAPBOX IN THIS VENUE AS WELL.

DR. LEVITT: THAT'S GREAT. THANK YOU.

CHAIRMAN GOLDSTEIN: OKAY. THANK YOU, DR. NEALE. WE'LL COME BACK TO ANOTHER ROUND OF DISCUSSION AFTER WE HEAR FROM MY COLLEAGUE DR. SEBAT. SO, JONATHAN, YOU READY TO GO?

DR. SEBAT: I'M READY TO GO. CAN YOU SEE MY MAIN SCREEN WITH MY TITLE SLIDE?

CHAIRMAN GOLDSTEIN: YES.

DR. SEBAT: YOU SEE MY TITLE SLIDE. OKAY. GREAT.

THE LAST COUPLE OF QUESTIONS FROM DRS. GOLDSTEIN AND LEVITT WERE ACTUALLY A GREAT SEGUE TO THIS PRESENTATION. AS DR. LEVITT ASKED, YOU WERE

ASKING ABOUT GENETIC MODIFIERS. AND THAT COMPLEXITY OF GENETIC MODIFIERS IS A MAJOR TOPIC THAT I'LL BE TALKING ABOUT. ALSO, DR. GOLDSTEIN'S QUESTION ABOUT NEURODEGENERATIVE AND NEURODEVELOPMENTAL, THERE ACTUALLY ARE A NUMBER OF EXAMPLES WHERE DIFFERENT MUTATIONS GAIN-OF-FUNCTION AND LOSS-OF-FUNCTION IN THE SAME GENE; FOR EXAMPLE, FMR1 CAN CAUSE NEURODEVELOPMENTAL OR NEURODEGENERATIVE DISEASE. WHEREAS, FXTAS NEURODEGENERATIVE DISEASE IS ASSOCIATED WITH GAIN-OF-FUNCTION OF FMR1. NEURODEVELOPMENTAL DISORDER IS ASSOCIATED WITH LOSS-OF-FUNCTION OF FMR1. SO THIS OVERLAP BETWEEN DISORDERS IS VERY MUCH REAL, AND IT'S VERY MUCH DEPENDENT ON THE DIFFERENT TYPE OF FUNCTIONAL EFFECT IN THE GENE. SO UNDERSTANDING A VARIETY OF FUNCTIONAL EFFECTS ON THE SAME GENE IS GOING TO BE CRITICAL IN TRANSLATIONAL STUDIES OF GENETIC FINDINGS.

SO LET ME DIVE RIGHT INTO IT HERE. SO I'LL GO QUICK THROUGH THE GENE DISCOVERY BECAUSE THE GENE DISCOVERY PARTS OF IT IS JUST HOW -- JUST THE FIRST STAGE OF GENETICS. YOU FIND THE GENES AND THEN WHAT? SO THE GENOMEWIDE ASSOCIATION STUDIES OF SCHIZOPHRENIA HAVE BEEN OVERWHELMINGLY SUCCESSFUL IN IDENTIFYING CREDIBLE ASSOCIATIONS THROUGHOUT THE

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GENOME. OF COURSE, EACH ONE OF THESE ARE INDIVIDUAL SNP'S OF VERY SMALL EFFECTS, BUT COLLECTIVELY THEY ACTUALLY CARRY SIGNIFICANT RISK, AND COLLECTIVELY THEY CAN TELL YOU SOMETHING ABOUT THE UNDERLYING MECHANISMS THROUGH WHICH THE GENETIC RISK ACTS. FOR EXAMPLE, THESE COMMON VARIANTS ARE ENRICHED IN SPECIFIC CELL TYPES; FOR EXAMPLE, PYRAMIDAL NEURONS, MEDIUM SPINY NEURONS, INTERNEURONS. AND THEN, OF COURSE, AS BEN MENTIONED, SYNAPTIC GENES ARE WELL REPRESENTED AMONG THESE TOP HITS. AND SO KIND OF COMPONENTS OF THE SYNAPSE THAT ARE INVOLVED IS ALSO COMING FROM COMMON VARIANTS, WHICH IS VERY ENCOURAGING.

OF COURSE, BEN TALKED ABOUT SCHEMA WHERE THE RARE VARIANTS IN SCHIZOPHRENIA ARE THE FOCUS. AND, OF COURSE, THE RARE CODING VARIANTS ARE VERY STRONGLY ASSOCIATED, AND ALSO THEY IMPLICATE SPECIFIC GENES. AND NOT ONLY THAT, BUT THEY IMPLICATE SPECIFIC VARIANTS THAT CAN BE MODELED IN CELLS AND IN ANIMALS TO ACTUALLY MODEL THE EFFECTS OF THAT GENE AND TRY TO UNDERSTAND WHAT EFFECT IT'S HAVING ON THE CIRCUITS AND HOW THAT MIGHT RELATE TO PSYCHIATRIC DISORDERS.

AN IMPORTANT THING TO EMPHASIZE, THOUGH, AT LEAST IN A CASE CONTROL STUDY, THE EXOMES ARE

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LARGELY FINDING THE LOSS-OF-FUNCTION VARIANTS. AND THE GAIN-OF-FUNCTION VARIANTS ARE STILL SOMEWHAT BURIED. THE MISSENSE VARIANTS HAVE VERY WEAK EFFECTS, AND IT'S A COMBINATION OF GAIN- AND LOSS-OF-FUNCTION, MAKING THE DISCOVERY OF THOSE VARIANTS A LITTLE MORE DIFFICULT WHEN YOU'RE JUST COLLAPSING ALL THE MISSENSE VARIANTS INTO ONE PILE AND TESTING THEIR ASSOCIATION.

SO WE ARE NOT IDEALLY DESIGNED FOR CAPTURING OTHER TYPES OF VARIANTS, BUT LOSS-OF-FUNCTION IS VERY EASY TO CAPTURE. AND THAT'S WHERE WE SEE THE MOST SIGNAL AND WHERE THE HERITABILITY SEEMS TO BE CONCENTRATED. BUT, AGAIN, I THINK TO SOME EXTENT IT HAS TO DO WITH THE LAMPPOST THAT WE ARE LOOKING UNDER.

AGAIN, IN AUTISM THERE ARE HUNDREDS OF HIGH CONFIDENCE AUTISM GENES THAT HAVE BEEN IDENTIFIED FROM EXOME SEQUENCING. AND BY FAR MOST OF WHAT WE KNOW ABOUT THE BIOLOGY OF AUTISM IS COMING FROM THE RARE VARIANTS. BUT NOW WITH THE TRIO-BASED APPROACH, WHERE YOU'RE NOT SO RESTRICTED ON YOUR ABILITY TO COLLAPSE ALL THE VARIANTS INTO A SINGLE CATEGORY AND TEST THEIR ASSOCIATION, IF YOU CAN BE A LITTLE LESS DEPENDENT ON THAT, THEN YOU START TO CAPTURE GAIN-OF-FUNCTION MUTATIONS AS WELL.

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SO WE SEE THAT THERE'S A COMBINATION OF LOSS-OF-FUNCTION AND PROTEIN-TRUNCATING VARIANTS AND DELETIONS THAT DOMINATE SCN2A, SHANK3, AND, IN FACT, MOST OF THE GENES ON THE LIST ARE DOMINATED BY PROTEIN-TRUNCATING VARIANTS OR DELETIONS.

BUT AS YOU SEE ON THE RIGHT, YOU CAN ACTUALLY SEE THERE'S A FEW THINGS STARTING TO SHOW UP WHERE THE PREDOMINANT ALLELES ARE EITHER DUPLICATIONS OR MISSENSE VARIANTS LIKE P10 AND SCL6A1. SO NOW WE ARE STARTING TO SEE GAIN-OF-FUNCTION VARIANTS STARTING TO BE A BIGGER FACTOR. AND, OF COURSE, MISSENSE VARIANTS OUTNUMBER PROTEIN-TRUNCATING VARIANTS BY A HUGE MARGIN. AND IF WE HAD BETTER WAYS OF DIGGING DEEPER INTO THAT MISSENSE PILE, I THINK THERE'S A LOT MORE TO BE DISCOVERED.

NOW, THESE RARE VARIANTS CONVERGE ON NEURODEVELOPMENTAL PATHWAYS. I'M HIGHLIGHTING HERE AUTISM IN PARTICULAR. AND, OF COURSE, THIS IS SYNAPTIC CHROMATIN REMODELING GENES AND POST-TRANSCRIPTIONAL REGULATION. BUT YOU COULD COMPLETELY SWITCH AUTISM AND SCHIZOPHRENIA IN HERE, AND YOU'D BASICALLY BE FINDING THE SAME PATHWAYS. SO JUST AT A BROAD LEVEL, WHAT PATHWAYS ARE INVOLVED IS NOT ENOUGH. IT'S NOT ENOUGH TO TELL YOU WHAT IS

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AUTISM BECAUSE I DON'T THINK AUTISM AND SCHIZOPHRENIA ARE DISTINGUISHABLE VERY CLEARLY JUST BY GROUPING THINGS INTO PATHWAYS. YOU REALLY NEED TO UNDERSTAND HOW THE PATHWAYS ARE ALTERED TO REALLY MAKE SENSE OF IT ALL.

SO AUTISM GENES ARE, OF COURSE, ENRICHED IN DEVELOPING CORTEX. GWAS GENES ARE ENRICHED IN THE DEVELOPING CORTEX AND THE EXOME GENES ARE WAY ENRICHED. SO THE MAGENTA LINE HERE IS SHOWING THE TRAJECTORY OF EXPRESSION OF THESE EXOME GENES ACROSS DEVELOPMENT. AND EARLY FETAL EXPRESSION OF THOSE GENES IS HIGHLY ENRICHED.

AT THE INDIVIDUAL CELL TYPES, IT'S NEURONS, NEURONS, NEURONS. SO EITHER PROGENITOR CELLS OR MATURING EXCITATORY NEURONS OR EXCITATORY DEEP LAYER NEURONS ARE WHERE THE EXOME FINDINGS ARE SIGNIFICANTLY ENRICHED.

YOU LOOK OFF TO THE RIGHT, THOSE OF YOU WHO ARE REALLY EXCITED ABOUT GLIA, MICROGLIA IS THERE TOO. IT JUST DOESN'T REACH SIGNIFICANCE AFTER MULTIPLE TEST DIRECTION HERE, BUT MICROGLIA IS ALSO PROBABLY A FACTOR. IT'S JUST NOT WHERE THE EXOME DATA IS MOST STRONGLY CONCENTRATED. THEY'RE MOST STRONGLY CONCENTRATED IN DEVELOPING NEURONS.

SO I WANT TO EMPHASIZE HERE GENE

DISCOVERY, FINDING THE LIST OF GENES AND THEN GIVING UP AT THAT POINT, IF YOU WERE A STATISTICIAN, THAT'S HOW YOU WOULD APPROACH GENETICS. BUT LIKE ME OR BIOLOGISTS, THAT'S JUST THE START. YOU NEED TO UNDERSTAND THE GENETIC MECHANISMS BETTER. YOU CAN'T JUST FIND THE GENES AND THEN TURN AROUND AND MOVE ON TO THE NEXT DISEASE.

SO WE HAVE TO LOOK AT HOW GENES ARE ACTUALLY RELATING TO TRAITS. THIS IS A RECENT PAPER FROM OUR GROUP LOOKING AT RARE VARIANTS AND COMMON VARIANTS AND HOW THEY IMPACT THE PHENOTYPE SPECTRUM OF AUTISM. AND THIS IS JUST A HEAT MAP OF PHENOTYPES, REPETITIVE BEHAVIOR, SOCIAL BEHAVIOR, ADAPTIVE BEHAVIOR. AND ON THE COLUMNS YOU HAVE DIFFERENT CATEGORIES OF VARIATIONS. SO RARE, DE NOVO, MISSENSE, LOSS-OF-FUNCTION, OR POLYGENIC SCORES FOR AUTISM, SCHIZOPHRENIA, AND EDUCATION.

AND WHAT YOU CAN SEE HERE IS THAT ALL THINGS ARE NOT EQUAL. IN FACT, THESE DIFFERENT GENETIC PREDICTORS ACTUALLY HAVE VERY DIFFERENT PHENOTYPIC CORRELATES. SO IF YOU FOCUS JUST ON THE SOCIAL DEFICITS, IT'S ENCOURAGING TO SEE THAT DE NOVO LOSS-OF-FUNCTION AND THE POLYGENIC SCORE FOR AUTISM ARE CORRELATING WITH SOCIAL COMMUNICATION DEFICITS AND SOCIAL RESPONSIVENESS DEFICITS. THAT'S

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VERY ENCOURAGING. IT MEANS THAT GENETICS IS WORKING, AND IT'S ACTUALLY FINDING THINGS THAT ARE RELATED TO SOCIAL BEHAVIOR.

BUT IF YOU LOOK AT OTHER ASPECTS OF THE SPECTRUM OF AUTISM, IT'S INTERESTINGLY REPETITIVE BEHAVIOR, NOT REALLY AUTISM POLYGENIC SCORES AND DE NOVOS FOR WHATEVER REASON ARE NOT REALLY MOVING THE NEEDLE ON REPETITIVE BEHAVIOR, BUT SOMEHOW THE POLYGENIC SCORE FOR EDUCATION IS THE STRONGEST INFLUENCE ON REPETITIVE BEHAVIOR IN CASES. OF COURSE, YOU CAN SEE THE SAME THING IS HAPPENING IN CONTROLS AS WELL AS IN CASES. SO THESE FACTORS AREN'T RESTRICTED TO CASES. YOU CAN SEE SIMILAR EFFECTS IN CASES AND CONTROLS, AND YOU SEE IT IN THEIR PARENTS. SOCIAL BEHAVIOR IN PARENTS IS ALSO IMPACTED BY THE SAME GENETIC FACTORS THAT ARE INFLUENCING SOCIAL BEHAVIOR IN THE CHILDREN. AND, OF COURSE, MOTOR FUNCTION IS EXCLUSIVELY A RARE VARIANT FACTOR. RARE VARIANTS ARE INFLUENCING MOTOR FUNCTION.

NOW, GENE-BY-SEX INTERACTIONS ARE SOMETHING WE CAN START TO EXPLORE AS WELL. AND WHAT WE ARE SEEING IS THAT THEY GO BOTH WAYS. SO IN AUTISM YOU WOULD THINK, OH, GENETIC FACTORS MUST HAVE A MALE-BIASED EFFECT BECAUSE AUTISM IS A

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MALE-BIASED DISORDER. WELL, YES, THAT'S PROBABLY TRUE. IN FACT, YOU CAN SEE THAT THE POLYGENIC SCORE FOR AUTISM, IT DOES HAVE A MALE-BIASED EFFECT ON SOCIAL COMMUNICATION. BUT OTHER THINGS ARE FEMALE BIASED LIKE THE POLYGENIC SCORE FOR SCHIZOPHRENIA AND EDUCATION SEEM TO HAVE A FEMALE-BIASED EFFECT IN CERTAIN TRAITS. AND ALL OF THESE GENETIC FACTORS ARE CORRELATED WITH THE AGE AT WHICH PARENTS DECIDE TO HAVE CHILDREN.

SO THIS IDEA OF OLDER FATHERS ARE MORE LIKELY TO HAVE A CHILD WITH AUTISM, THAT'S VERY MUCH CONNECTED WITH THE GENETIC RISK THAT OLDER MOTHERS AND OLDER FATHERS CARRY. BUT, AGAIN, THE DIFFERENCE IN THESE FACTORS HAVE A VERY DIFFERENT SEX BIAS IN SOME CASES. SO WHAT'S MAKING MOTHERS OLDER MAY BE A DIFFERENT GENETIC PREDICTOR THAN WHAT'S MAKING FATHERS OLDER.

SO WE WANT TO FOCUS IN ON -- THE RARE VARIANTS, OF COURSE, ARE A BIG FOCUS BECAUSE THESE ARE THE EASIEST THINGS TO MODEL IN IPS CELLS OR IN ANIMALS. AND SO THAT'S A BIG FOCUS IN MY LAB. BUT, OF COURSE, IF YOU WANT TO UNDERSTAND HOW DOES THAT GENE OR THAT RARE VARIANT IMPACT THE CELLS AND NEURAL CIRCUITRY AND HOW DOES THAT RELATE TO PSYCHIATRIC TRAITS, YOU ACTUALLY HAVE TO STUDY THE

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PSYCHIATRIC TRAITS OF THESE CNV CARRIERS. JUST LABELING THE DIAGNOSIS THAT'S CONNECTED TO A GENE IS PROBABLY NOT SUFFICIENT. YOU REALLY HAVE TO UNDERSTAND THE MAIN EFFECTS OF THAT RARE VARIANT ON HUMAN TRAITS AND CELLULAR AND CIRCUITRY.

SO COPY NUMBER VARIANTS ARE PARTICULARLY USEFUL HERE BECAUSE, A, THEY ARE MUCH, MUCH MORE COMMON THAN GENE MUTATIONS BY AN ORDER OF MAGNITUDE. SO IF YOU WANT TO HAVE GOOD POWER TO LOOK AT CLINICAL DATA IN HUMANS, THE CNV'S ARE THE BEST BANG FOR YOUR BUCK. YOU CAN GET HUNDREDS OF INDIVIDUALS WITH THE SAME COPY NUMBER VARIANT. AND THESE HAVE QUANTITATIVE EFFECTS ON TRAITS, GENE EXPRESSION BECAUSE THEY OCCUR AS BOTH DELETION AND IN DUPLICATIONS MUCH OF THE TIME.

SO HERE'S JUST AN EXAMPLE OF BODY MASS, HEAD CIRCUMFERENCE, CORTICAL THICKNESS. IN ALL OF THESE CASES, THE 16P DEL AND DUP HAVE MIRROR OPPOSITE EFFECTS ON CORTICAL THICKNESS, BRAIN VOLUME, AND BODY MASS. SO THESE EFFECTS ARE IN OPPOSITE DIRECTIONS. AND THAT'S, AGAIN, A RECURRING THEME HERE. AND MODELING THESE EFFECTS SHOWS THAT, EVEN IN CELLULAR MODELS, YOU CAN HAVE THE DIAMETRICALLY OPPOSITE EFFECTS OF A DELETION OF A GENE VERSUS DUPLICATION OF A GENE. SO THOSE SAME

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CNV'S, BASICALLY THESE EFFECTS OF HUMAN BRAIN DEVELOPMENT CAN BE RECAPITULATED IN CORTICAL ORGANOID MODELS. SO THIS IS DONE BY LILIA LAKOUCHEVA HERE AT UCSD.

BUT, AGAIN, WE NEED TO UNDERSTAND HOW DOES THAT RELATE TO TRAITS. SO BY DEEP PHENOTYPING THESE RARE CNV'S IS PROBABLY ONE VALUABLE WAY THAT WE CAN START TO CONNECT THE CELLULAR PHENOTYPES THAT MIGHT BE TURNED UP IN MODEL SYSTEMS WITH THE ACTUAL HUMAN TRAITS AND HUMAN BRAIN CIRCUITRY.

SO THIS IS A GENES TO MENTAL HEALTH NETWORK THAT'S TRYING TO RECRUIT LARGE SAMPLES OF RARE DISEASE. SO OUR TARGET IS ABOUT 500 PER DISORDER STARTING WITH 16P11.2 AND 22Q11.2. AND ONE THING YOU CAN SEE IS THAT, WHEN YOU HAVE THESE LARGE COHORTS, NOT ONLY CAN YOU SEE THE MAIN EFFECT OF THE RARE VARIANT, BUT YOU CAN ALSO SEE THE MODIFYING EFFECT ON POLYGENIC SCORE. SO IN THIS CASE YOU HAVE A DELETION OF 22Q11.2, WHICH HAS A 25-PERCENT RISK OF SCHIZOPHRENIA. THAT'S MASSIVE COMPARED TO JUST ABOUT ANYTHING ELSE THAT'S OUT THERE. BUT IF YOU LOOK AT THE POLYGENIC SCORE FOR SCHIZOPHRENIA IN THOSE CARRIERS, YOU CAN SEE THAT, DEPENDING ON THE POLYGENIC SCORE, YOU COULD HAVE MUCH LOWER RISK. YOU MAY HAVE ONLY 10-PERCENT RISK OF SCHIZOPHRENIA

IF YOU HAVE THE LOWEST DECILE OF POLYGENIC SCORE. AND IF YOU HAVE THE HIGHEST DECILE OF POLYGENIC SCORE, YOU CAN BE BETWEEN 30- AND 40-PERCENT RISK OF SCHIZOPHRENIA.

SO HOW THAT DELETION IS INTERACTING WITH THE POLYGENIC BACKGROUND IS PRETTY IMPORTANT. AND ACTUALLY THE POLYGENIC SCORE FOR IQ IS AN EVEN BIGGER PREDICTOR. DEPENDING ON YOUR DECILE OF IQ POLYGENIC SCORE, YOU COULD HAVE A POSITIVE PREDICTIVE VALUE OF ONLY 20 PERCENT FOR INTELLECTUAL DISABILITY. OR IF YOU HAVE THE TOP DECILE OF THE POLYGENIC SCORE, YOU HAVE A 60-PERCENT POSITIVE PREDICTIVE VALUE FOR INTELLECTUAL DISABILITY. SO, AGAIN, THE POLYGENIC BACKGROUND IS CRITICAL IN UNDERSTANDING WHAT'S GOING ON IN ADDITION TO WHAT AN INDIVIDUAL GENE OR POLYGENIC SCORE IS INFLUENCING.

SO HERE IN THE -- THE CNV'S ARE USED FOR A VARIETY OF OTHER REASONS AS WELL. AND IMPORTANTLY, THE DISSECTING OF THE EFFECTS OF GENES ON PSYCHIATRIC TRAITS AND HOW THAT'S CONCENTRATED IN PATHWAYS, CELLS, AND THE BRAIN ARE CRITICAL.

SO WE ARE DOING THESE WELL-POWERED STUDIES OF CNV'S ACROSS MULTIPLE DISORDERS TO REALLY START TO UNDERSTAND HOW THE DELETION/DUPLICATION EFFECTS ON GENES ARE CONCENTRATED IN PATHWAYS ACROSS THESE

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DIFFERENT TRAITS. AND THESE ARE LARGE COHORTS OF AUTISM, SCHIZOPHRENIA, PTSD, MAJOR DEPRESSION, BIPOLAR DISORDER AND WHERE COPY NUMBER VARIANTS CAN BE DETECTED FROM GWAS, WHICH GIVES YOU REALLY WELL-POWERED STUDIES OF RARE VARIANTS. SO THESE RARE VARIANTS ARE ASSOCIATED -- THIS IS THE CROSS-DISORDER ASSOCIATION ANALYSIS.

SO THE COLOR OF THE TRIANGLE INDICATES THE DISORDER THAT IT'S ASSOCIATED WITH, AND THE DIRECTION OF THE TRIANGLE INDICATES THE DIRECTION OF THE EFFECT. SO NOT ONLY DO YOU HAVE RISK FACTORS THAT ARE RARE, BUT YOU ALSO HAVE PROTECTIVE VARIANTS THAT ARE RARE. FOR EXAMPLE, ON 22Q THE DELETION IS INCREASING YOUR RISK OF SCHIZOPHRENIA, BUT THE DUPLICATION IS DECREASING YOUR RISK FOR SCHIZOPHRENIA. SO YOU HAVE DIRECTIONALITY OF THE EFFECT IS CRITICAL, AND UNDERSTANDING BOTH DIRECTIONS IS ALSO CRITICAL.

OF COURSE, WHEN YOU FOCUS IN ON THESE AND LOOK ACROSS THE RANGE OF DISORDERS, WHAT YOU CAN SEE IS THAT CERTAIN GENES OR REGIONS ARE PREDOMINANTLY AUTISM RISK FACTORS. FOR EXAMPLE, THE DUPLICATIONS ON CHROMOSOME 15Q11 TO 13 IS PREDOMINANTLY AN AUTISM RISK FACTOR. AND TO A LESSER EXTENT, YOU CAN SEE RISK FOR SCHIZOPHRENIA, MAJOR DEPRESSION, BIPOLAR

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DISORDER.

OTHER DELETIONS NEARBY, IT'S PLENTY OF RISK FACTORS ARE THE PREDOMINANT ASSOCIATION THAT YOU SEE WITH THE DELETIONS THAT FLANK THIS REGION. AGAIN, THEY'RE DIFFERENT GENES. BUT OVER HERE YOU HAVE A VARIETY OF REGIONS THAT ARE ASSOCIATED, AND IN SOME CASES YOU ACTUALLY HAVE THE SAME REGION, BUT YOU HAVE DIFFERENCES WHETHER THERE'S A DUPLICATION OR A DELETION, AND FOR 16P, THE DUPLICATION IS THE SCHIZOPHRENIA RISK FACTOR AND THE DELETION IS THE AUTISM, MAJOR AUTISM ASSOCIATION. IT'S AT THE OPPOSITE OF 22Q. 22Q, THE DELETION WAS THE SCHIZOPHRENIA RISK FACTOR AND THE DUP WAS PROTECTIVE. IT GOES THE OTHER WAY WITH CHROMOSOME 16. IT'S THE DUP THAT'S THE SCHIZOPHRENIA RISK FACTOR AND THE DEL IS NOT ASSOCIATED WITH SCHIZOPHRENIA.

SO AS BEN MENTIONED, CNV'S ARE A LITTLE HARDER TO INTERPRET FROM THE STANDPOINT OF WHAT GENE IS INVOLVED. THERE ARE 30 DIFFERENT GENES IN THIS REGION. SO WHAT IS THE GENE? BUT THAT'S EXACTLY NOT THE QUESTION. THE WHOLE POINT IS THAT YOU'RE NOT PINPOINTING INDIVIDUAL GENES BECAUSE SCHIZOPHRENIA IS NOT A SINGLE-GENE DISORDER. THE REASON WHY THESE THINGS HAVE LARGER EFFECTS THAN

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INDIVIDUAL GENE MUTATIONS IS PRECISELY BECAUSE THEY HAVE AN OLIGOGENIC EFFECT THAT'S DISTRIBUTED ACROSS 30 DIFFERENT GENES, AND THERE'S PROBABLY MORE THAN ONE GENE CONTRIBUTING TO THIS.

AND SO THE CNV'S ARE A GOOD WAY OF MEASURING HOW GENETIC LOADING IS DISTRIBUTED ACROSS LARGE NUMBERS OF GENES. SO THAT'S ACTUALLY WHAT WE ARE STARTING TO DO MORE OF, WHICH IS TO DO MORE GENE-SET ANALYSES AND TO MEASURE HOW THE GENETIC LOADING ACROSS PATHWAYS, CELL TYPES, BRAIN REGIONS IS ASSOCIATED WITH DISORDERS. AND BY LOOKING ACROSS DISORDERS, YOU CAN LOOK AT HOW PATHWAY, CELL TYPES, AND BRAIN REGIONS DIFFER BETWEEN AUTISM, SCHIZOPHRENIA, MAJOR DEPRESSION AND HOW THEY DIFFER BETWEEN A GAIN-OF-FUNCTION AND LOSS-OF-FUNCTION.

SO I'M JUST GOING TO TOUCH ON SOME INTRIGUING RESULTS, UNPUBLISHED, FROM THE LATEST STUDY, AND THEN I'LL OPEN IT UP FOR QUESTIONS. BUT BASICALLY HERE'S A VERY INTRIGUING RESULT WHICH WE'VE BEEN SORT OF DANCING AROUND FOR A FEW YEARS, BUT NOW IT'S REALLY CLEAR IS THAT SCHIZOPHRENIA HAS A DIRECTIONAL EFFECT ON SPECIFIC PATHWAYS AND BRAIN REGIONS. AND THE WAY YOU KNOW THIS IS THAT THE EFFECT SIZE OF DELETION IN A PARTICULAR PATHWAY IS INVERSELY CORRELATED WITH THE EFFECT SIZE OF THE

DUPLICATION ON THE SAME PATHWAY.

SO THERE ARE PATHWAYS THAT ARE STRONGLY ASSOCIATED WITH DELETION AND WEAKLY ASSOCIATED WITH DUPS. AND BY CONTRAST, THERE'S PATHWAYS THAT ARE STRONGLY ASSOCIATED WITH DUPS AND WEAKLY ASSOCIATED WITH DELS. AND OVERALL, BOTH WITH PATHWAYS AND CORTICAL BRAIN REGIONS FROM ALLEN BRAIN ANALYSTS, YOU CAN SEE THAT THESE GENE SETS HAVE A NEGATIVE -- A SIGNIFICANT NEGATIVE CORRELATION OF DEL EFFECT VERSUS DUP EFFECT.

AND IF YOU LOOK AT WHAT THE BRAIN REGIONS ARE, YOU CAN SEE THAT IT'S, WELL, AT LEAST FOR DUPLICATION, IT'S VERY BROADLY EXPRESSED. AND THE DUPLICATION SIGNAL IS REALLY STRONG, BUT IT DOES SEEM TO BE PRETTY WELL CONCENTRATED IN THE PREFRONTAL CORTEX, SOMATOSENSORY CORTEX, MAYBE VISUAL CORTEX. AND THEN IF YOU LOOK AT THE DELETION, REALLY VERY DIFFERENT PATTERN, ALTHOUGH IT'S WEAKER, BUT THERE'S REALLY LESS PREFRONTAL CORTEX ACTION GOING ON IN THE DELETION SIGNAL THAN IN THE DUPLICATION SIGNAL.

I WOULDN'T GO SO FAR AS TO SAY THAT DELETIONS AREN'T IMPACTING THE PREFRONTAL CORTEX. I'M JUST SAYING THAT, IN TERMS OF THE PATHWAYS AND BRAIN REGION THAT WE ARE LOOKING AT, REALLY THERE'S

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GAIN-OF-FUNCTION SIGNAL THERE AND LESS LOSS-OF-FUNCTION SIGNAL.

AND THE CELL TYPES THAT WE ARE LOOKING AT, WE ARE NOTICING THAT EARLY FETAL STAGE PROGENITOR CELLS, EXCITATORY DEEP LAYER NEURONS ARE ASSOCIATED WITH DUPLICATION AT THE CELL TYPE LEVEL. AND DELETION, A LITTLE BIT MORE POSTNATAL AND MATURING EXCITATORY NEURONS. SO WE ARE SEEING A LITTLE MORE EARLY FETAL VERSUS LATE FETAL, POSTNATAL WHEN WE LOOK AT DUPS VERSUS DELS. AND WHEN WE LOOK AT PATHWAYS, THE DUPS ARE SHOWING MORE REGULATORS OF HISTONE MODIFICATION TRANSCRIPTION, TRANSLATION, THAT KINASE SIGNALING; WHEREAS, THE DELS, THAT'S WHERE THE SYNAPSE SIGNAL IS. SO WE HAVE MORE POST-SYNAPTIC DENSITY. NEUROLIG AND NEUREXINS, LIPID TRANSPORT, WHICH IS POTENTIALLY RELATED TO VESICLE EXOCYTOSIS AND OTHER THINGS.

SO THE LOSS-OF-FUNCTION VARIANTS AND THE SYNAPTIC VARIANTS, I WOULD REALLY SAY IT'S JUST PART OF THE STORY. AND IT'S REALLY THIS LOSS-OF-FUNCTION STORY, AND IT'S PROBABLY IMPACTING ONLY A SUBSET OF PATHWAYS AND BRAIN REGIONS. WHEREAS, THERE ARE OTHER FACTORS THAT ARE MORE REGULATORILY EARLY FETAL THAT ARE AFFECTING OTHER BRAIN REGIONS IN A DIFFERENT WAY, PRESUMABLY.

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SO AUTISM, DIFFERENT STORY. SO THESE SAME PATHWAY RELATIONSHIPS GO THE OTHER WAY IN AUTISM. WHERE DELS AND DUPS, THEY GENERALLY AFFECT THE SAME PATHWAYS, BUT IN DIFFERENT DIRECTIONS, BUT EITHER DIRECTION IS AUTISM ASSOCIATED. SO AUTISM HAS GOT A VERY DIFFERENT KIND OF PATTERN HERE, BUT IT LOOKS LIKE -- BASICALLY IT LOOKS LIKE GAIN OR LOSS IS AN AUTISM RISK FACTOR. SO IT'S NOT QUITE AS DIRECTIONAL IN AUTISM COMPARED TO SCHIZOPHRENIA.

NOW, WHEN YOU ACTUALLY LOOK AT THE PATHWAYS AND BRAIN REGIONS, SOMETHING THAT'S PARTICULARLY STRIKING IS THAT, WAIT A MINUTE, WE ARE SEEING, AT LEAST FROM MY HUMAN VISUAL PATTERN RECOGNITION SOFTWARE I GOT GOING ON IN MY BRAIN, I WOULD LOOK AT THESE TWO PLOTS AND SAY, WELL, THESE KIND OF LOOK SIMILAR. WHAT'S GOING ON HERE? WELL, IF YOU LOOK AT SCHIZOPHRENIA DUPLICATION AND AUTISM DELETION, BOOM. YOU ACTUALLY HAVE THIS POSITIVE CORRELATION WHERE THE LOSS-OF-FUNCTION IN AUTISM IS ASSOCIATED WITH GAIN-OF-FUNCTION IN SCHIZOPHRENIA. AND THIS IS REALLY KIND OF INTRIGUING, AND IT'S TRUE ACROSS PATHWAYS, CELL TYPES, AND BRAIN REGIONS. NOT EVERY PATHWAY, BUT THERE IS A SPECIFIC SUBSET OF PATHWAYS THAT SEEM TO HAVE THIS RELATIONSHIP.

SO THIS KIND OF PINPOINT -- THIS KIND OF

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LEANS TOWARDS SOME THEORIES THAT HAVE BEEN AROUND IN THE PSYCHIATRY FIELD FOR A LONG TIME, THAT THESE DIFFERENT DISORDERS ACTUALLY HAVE COMMON UNDERLYING PROCESSES, BUT DIAMETRICALLY OPPOSED. SO BERNARD CRESPI HAS A REALLY NICE SERIES OF THEORETICAL PAPERS WHERE HE KIND OF SPECULATES A LOT ON THIS TOPIC. AND THIS ONE IS ONE THAT CAUGHT MY EYE AND I THOUGHT WAS REALLY INTERESTING.

SO IN TERMS OF PATHOLOGY IN THE BRAIN, THERE IS PATHOLOGY, BUT IT'S VERY CRUDE. IN THE CASE OF AUTISM, YOU HAVE INCREASED BRAIN VOLUME, INCREASED CORTICAL THICKNESS. IN THE CASE OF SCHIZOPHRENIA, YOU DO HAVE DIAMETRICALLY OPPOSED PHENOTYPES ON THOSE PARTICULAR TRAITS. YOU HAVE ON AVERAGE DECREASED BRAIN VOLUME AND DECREASED CORTICAL THICKNESS IN PSYCHOSIS. AND THIS IS SOMETHING THAT PEOPLE HAVE PICKED UP ON AND BERNARD KIND OF HIGHLIGHTED.

ON THE BEHAVIORAL LEVEL YOU KIND OF SEE SOMETHING ALONG THE SAME LINES WHERE COGNITION, FOR EXAMPLE, IN CERTAIN TRAITS, A GAZE, INDIVIDUALS WITH AUTISM HAVE LESS SENSITIVITY TO GAZE FROM OTHERS, A LITTLE BIT LESS ENGAGEMENT, FOR EXAMPLE. WHEREAS, SCHIZO PSYCHOSIS, HIGH SENSITIVITY TO THE GAZE OF OTHERS AND TO SOME EXTENT PARANOIA ABOUT OTHERS

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LOOKING OR THINKING ABOUT YOU.

AND THEN THEORY OF MIND KNOWN TO BE REDUCED IN AUTISM; WHEREAS, THOUGHT TO BE ENHANCED IN SCHIZOPHRENIA. INTENTION, FAILURE TO RECOGNIZE OR UNDERSTAND INTENTION IS A PROBLEM WITH AUTISM. WHEREAS, IN SCHIZOPHRENIA YOU HAVE DELUSIONS OF OTHERS HAVING SINISTER INTENTIONS. AND REWARD MOTIVATION, SENSORY PROCESSING, IN AUTISM YOU HAVE DISCOMFORT WITH SENSORY STIMULI; WHEREAS, IN SCHIZOPHRENIA, YOU CAN HAVE A TENDENCY TO HAVE FREE OR LOOSE ASSOCIATION OF THE INCOMING STIMULI.

SO THESE DIAMETRICALLY OPPOSED PHENOTYPES ARE TRUE, A, AT THE GENETIC LEVEL; B, TO SOME EXTENT AT THE BRAIN VOLUME AND NEUROANATOMICAL LEVEL, AND PERHAPS TO SOME EXTENT AT THE TRAIT LEVEL AS WELL.

SO THIS IS A GOOD TIME TO WRAP UP. THESE IMPLICATIONS FOR TRANSLATIONAL STUDIES ARE ALONG THESE LINES. YOU CLEARLY HAVE ONE GENE THAT MAY HAVE STRONG INFLUENCE ON AUTISM, BUT THAT GENE BY ITSELF DOES NOT EXIST IN A VACUUM. IT'S PART OF A MULTIFACTORIAL ETIOLOGY. NOT ONLY THAT, THAT SAME GENE MAY ALSO CARRY RISK OF OTHER DISORDERS, AND DIFFERENT MUTATIONS IN THAT GENE MAY CARRY RISK OF OTHER EVEN DIAMETRICALLY OPPOSED TRAITS AND DISORDERS SO THAT WE WANT TO INTEGRATE.

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IN ORDER TO REALLY UNDERSTAND PSYCHIATRIC TRAITS, WE NEED TO INTEGRATE CLINICAL, CELL, AND CIRCUIT PHENOTYPES ACROSS MULTIPLE GENES AND CNV'S. AND, OF COURSE, THE MOST VALUABLE RESOURCES THAT ALLOW US TO DO THIS ARE THE BIG COHORTS THAT ARE BEING COLLECTED AND RELEASING PUBLICLY PHENOTYPE DATA, MOST IMPORTANTLY GENETIC DATA, EXOME AND GWAS. AND THEN, OF COURSE, IF YOU HAVE IPS CELLS OR DNA SAMPLES THAT YOU CAN RELEASE ON THOSE AS WELL. WE THINK THAT THIS IS ACTUALLY A GOOD -- THERE ARE GOOD OPPORTUNITIES FOR SYNERGY ACROSS THESE NIMH-DRIVEN CONSORTIA PROJECTS, RARE DISEASE IN COMMON, AND POTENTIALLY WITH OTHER AGENCIES THAT ARE DOING TRANSLATIONAL STUDIES.

THANK YOU.

CHAIRMAN GOLDSTEIN: THAT'S JUST GREAT, JONATHAN. THANK YOU VERY MUCH.

LET ME START A QUESTION THAT BEN MAY ALSO WANT TO ADDRESS, AND THAT IS TO WHAT EXTENT ARE THE POPULATION STUDIES REACHING INTO UNDERSERVED OR ECONOMICALLY DISADVANTAGED POPULATIONS? BECAUSE YOU MIGHT THINK THERE WOULD BE ENRICHMENT OF SOME OF THESE PROBLEMS IN THESE UNDERSERVED AREAS.

DR. SEBAT: SO GENETICS OBVIOUSLY HAS HAD A LONG-STANDING PROBLEM WITH BEING HEAVILY BIASED

TOWARDS POPULATIONS OF EUROPEAN ANCESTRY. AND MAYBE THAT WAS CONVENIENT IN THE BEGINNING WHEN YOU JUST NEEDED TO GET TO THOSE SAMPLE SIZES OF HUNDREDS OF THOUSANDS IN ORDER TO GET POWER TO FIND THESE GENES. THEN, YES, I GUESS IT WAS CONVENIENT TO FOCUS ON ONE ANCESTRY BECAUSE YOU CAN'T LUMP -- IT'S VERY DIFFICULT TO LUMP THEM ALTOGETHER. YOU YOU HAVE TO STUDY THEM SEPARATELY, AT LEAST IN THE BEGINNING.

BUT, OBVIOUSLY, NOW IT'S CLEAR THAT YOU'RE NOT GOING TO CAPTURE THE POLYGENIC SIGNAL FROM AFRICAN AND EAST ASIAN ANCESTRIES VERY WELL WITH SUMMARY STATISTICS FROM EUROPEAN GWAS. SO IT'S A PRIORITY OF THE NIMH TO START, AT LEAST WITH REGARD TO SAMPLE COLLECTION, IS REALLY STARTING TO EMPHASIZE NON-EUROPEAN ANCESTRIES IN THE COHORTS.

NOW, IN TERMS OF THE GENETIC MECHANISMS, I REALLY DON'T THINK THERE'S A STRONG -- WELL, THE GENETICS -- WELL, THE GENETIC BACKGROUNDS ARE DIFFERENT IN DIFFERENT ANCESTRIES, AND YOU CAN'T PREDICT WELL IN ASIAN AND AFRICAN ANCESTRIES WITHOUT DOING A GWAS IN THAT ANCESTRY. IT DOESN'T MEAN THAT THE GENETIC MECHANISMS ARE DIFFERENT. IT DOES MEAN THAT THOSE ARE DIFFERENT POPULATIONS THAT ARE GEOGRAPHICALLY DIFFERENT AND ENVIRONMENTALLY DIFFERENT BOTH IN TERMS OF SOCIOECONOMIC STATUS,

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ENVIRONMENTAL EXPOSURE.

SO THERE'S A LOT, WHEN YOU THINK ABOUT GENE ENVIRONMENT INTERACTION, THAT YOU COULD START TO THINK ABOUT WHEN YOU -- AND HOW THINGS MAY BE A DIFFERENT CHALLENGE IN A LATINO POPULATION, ASIAN, OR AFRICAN.

CHAIRMAN GOLDSTEIN: SOUNDS LIKE THERE'S A LOT OF WORK TO DO TO RECTIFY THAT PROBLEM.

DR. NEALE: I'D ADD JUST A FEW, I GUESS, ADDITIONAL PIECES OF NUANCE. HEALTHCARE UTILIZATION VARIES ACROSS LOTS OF DIFFERENT GROUPS OF PEOPLE FOR LOTS OF DIFFERENT REASONS. AND UNDERSERVED GROUPS THAT AREN'T WELL ENGAGED WITH THE HEALTHCARE SYSTEM ARE GOING TO BE UNDERREPRESENTED IN THESE KINDS OF STUDIES, AND THEY'RE ALSO -- I MEAN SO ONE OF THE LARGEST, MOST HIGH PROFILE BIOBANK EFFORTS IN THE WORLD IS SOMETHING CALLED THE UK BIOBANK. IT HAS HALF A MILLION PARTICIPANTS. THE RATE OF SCHIZOPHRENIA AS A DIAGNOSIS IN THAT COHORT IS, I THINK, A TENTH OF A PERCENT. AND THEN SCRUTINIZING THE SORT OF MATERIAL ASPECTS OF THOSE INDIVIDUALS AS IT PERTAINS TO, SAY, CLINICALLY RECRUITED GROUPS OF INDIVIDUALS WITH SCHIZOPHRENIA, IT'S OFTEN MUCH MORE MILD IN TERMS OF PRESENTATION AND MAY EVEN JUST BE A SORT OF ONE-OFF SORT OF DIAGNOSIS RATHER THAN BEING

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WHAT WE WOULD ADHERE TO IN THE CONTEXT OF RESEARCH STUDIES.

AND SO WITH THAT SORT OF MIND SETS WORK IN SCHIZOPHRENIA IN PARTICULAR, BUT IN SOME OF THE OTHER RELATED DISORDERS THAT CARRY WITH IT SEVERE BEHAVIORAL CONSEQUENCES SORT OF NECESSITATES THAT YOU FOCUS ON THOSE CLINICAL POPULATIONS. AND ONE OF THE THINGS THAT I GUESS I'M MOST GRATEFUL FOR IN TERMS OF WORKING ON THE PUMAS EFFORT IS PARTNERSHIP, AND PARTNERSHIP NOT JUST IN THE U.S., BUT ALSO PARTNERSHIP IN PLACES LIKE COLOMBIA WHERE THE RECRUITMENT FRAME IS LITERALLY EVERYONE IN AN INPATIENT PSYCHIATRIC FACILITY. AND THAT JUST SORT OF -- GOING TO INPATIENT PSYCHIATRIC FACILITIES IS WHERE YOU ARE GOING TO GET AMONG THE MOST SEVERE INDIVIDUALS, AND OFTEN THE BARRIERS TO ENTRY IN TERMS OF SOCIOECONOMIC STATUS OR OTHER HEALTHCARE UTILIZATION QUESTIONS ARE STILL PRESENT, BUT MORE MODERATED BECAUSE THE SEVERITY TRUMPS THE SORT OF RECRUITMENT ALONG THOSE LINES OF THOSE INDIVIDUALS INTO THAT KIND OF ENVIRONMENT. AND SO THAT DOES GO A PRETTY LONG WAY TO ADDRESSING SOME OF THESE LONGSTANDING INEQUITIES.

BUT IT IS, AS JONATHAN SAID, SOMETHING THAT THE NIMH HAD MADE A PRIORITY. PUMAS IS PART OF

SOMETHING CALLED THE ANCESTRAL POPULATIONS NETWORK WHERE THE EXPLICIT FOCUS OF THAT RFA WAS TO DIVERSIFY THE UNDERLYING COLLECTIONS. AND THERE ARE OTHER PROJECTS IN THAT NETWORK THAT NIMH IS SUPPORTING THAT ADDRESS OTHER ASPECTS AND DIMENSIONS.

AND THEN THE KIND OF FINAL THING I'D SAY ON THIS IS THE MOST EXTENSIVE INVESTIGATIONS IN THE COMMON VARIANT ANALYSIS OF SCHIZOPHRENIA HAVE FOCUSED ON INDIVIDUALS WITH BROADLY EUROPEAN GENETIC ANCESTRIES AND BROADLY EAST ASIAN GENETIC ANCESTRIES. AND IN THE CIRCUMSTANCE WHEREBY THE COMMON GENETIC VARIANT IS PRESENT IN BOTH GROUPS AND ASSOCIATED, IT SHOWS PRETTY SIMILAR EFFECTS. AND THAT SUGGESTS THAT OUR BIOLOGY IS SHARED BIOLOGY, OUR DISEASE BIOLOGY IS SHARED DISEASE BIOLOGY, AND THAT THESE APPROACHES WILL DELIVER, MAYBE NOT A KIND OF UNIVERSAL GUIDE TO HOW SOMEONE PRESENTS WITH THESE ILLNESSES, BUT THERE'S LIKELY TO BE MORE CONSISTENCY RATHER THAN DISSIMILARITY IN UNDERLYING DISEASE MECHANISM.

CHAIRMAN GOLDSTEIN: GREAT. THANK YOU. VERY INTERESTING. PAT.

DR. LEVITT: THANKS VERY MUCH, JONATHAN.

YOU JUST MADE IT MORE COMPLICATED. SO --

DR. SEBAT: ACTUALLY WHEN YOU GET BELOW SKIN DEEP, IT ALWAYS BECOMES MORE COMPLICATED.

DR. LEVITT: THAT'S CORRECT, YES.

DR. SEBAT: THE GENE LIST IS NICE BECAUSE IT WAS JUST A BUNCH OF GENE SYMBOLS.

DR. LEVITT: MY PERCEPTION IS THAT GENETICISTS KIND OF EMBRACE VARIATION AND VARIABILITY. YOU'RE TRYING TO SOLVE THE PUZZLE OF WHY THAT IS, RIGHT? AND YOU KNOW BOTH OF YOU PRESENTED THAT WITH TRANSPARENCY.

IN THE EXPERIMENTAL WORLD, WE TEND TO WANT TO FACTOR VARIATION OUT. AND SO I'M WONDERING HOW, GIVEN WHAT YOU BOTH SAID ABOUT VARIATION AND HETEROGENEITY, HOW YOU THINK WE SHOULD BE -- HOW YOU THINK WE SHOULD BE THINKING ABOUT THE PROGRAM THAT WE ARE GOING TO EMBARK UPON WHERE THERE'S GOING TO BE A LOT OF DISCOVERY AND YET WE ARE SORT OF EXPERIMENTALLY IN THIS MIND-SET OF VARIATION BEING A DEMON AS OPPOSED TO REFLECTING THE COMPLEXITY OF THE BIOLOGY, WHICH IS REFLECTED IN THE GENETICS.

DR. SEBAT: SO WHEN COLLEAGUES AND I HAVE GOTTEN TOGETHER FOR MARGARITAS AND BRAINSTORMED IDEAS FOR HOW DO WE MODEL THIS IN IPS CELLS IN A WAY THAT WOULD SOMEHOW GIVE US A REPRESENTATION OF HOW THE RARE VARIANT EFFECTS ARE WORKING AND HOW THE

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COMMON VARIANT EFFECTS ARE WORKING, AND I THINK THE BEST THING WE'VE KIND OF COME UP WITH IS THAT, WELL, ISOGENIC LINES OF RARE VARIANTS, VERY DOABLE AND EXTREMELY LARGE EFFECTS AND VERY MEASURABLE. AND THESE ARE BEAUTIFUL, SO LET'S STICK WITH THAT. LET'S STICK WITH THE RARE VARIANT EFFECTS. BUT IF THEY'RE ROBUST ENOUGH, WE SHOULD BE ABLE TO APPLY THEM TO ONE ISOGENIC LINE. AND NOW LET'S CHOOSE AN ISOGENIC LINE WITH VERY HIGH POLYGENIC RISK AND MAYBE A SERIES OF THEM AND LET'S USE SOME ISOGENIC LINES WITH VERY LOW POLYGENIC RISK FOR CERTAIN FACTORS. AND NOW TRY TO SEE IF THERE IS AN INTERACTION OR A DIFFERENCE IN THE OVERALL EFFECT BETWEEN THE HIGH GENETIC BACKGROUND AND THE LOW GENETIC BACKGROUND, FOR EXAMPLE.

OBVIOUSLY THE DREAM, BECAUSE THE BIOBANKS THAT HAVE REALLY BEEN THE MOST VALUABLE RESOURCES ARE THE ONES THAT DO COLLECT GENOMIC DATA AND SAMPLES ON REALLY LARGE COHORTS. SO THE DREAM, WHICH WOULD BE COST PROHIBITIVE MAYBE, I DON'T KNOW, BUT WOULD BE A COHORT STUDY WHERE YOU HAVE DEEP PHENOTYPE DATA AND CELLULAR PHENOTYPES. IF YOU CAN DO THAT TO THE EXTENT -- IN TERMS OF -- IF ALL YOU CARE ABOUT IS A POLYGENIC SCORE, THEN YOUR SAMPLE SIZES DO NOT NEED TO BE IN THE TENS OR HUNDREDS OF

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THOUSANDS. THE SAMPLE SIZES YOU NEED TO QUANTIFY POLYGENIC SCORE EFFECTS, IF THE EFFECT ON A TRAIT IS RELATIVELY LARGE, WOULD BE A FEW HUNDRED.

SO A COHORT STUDY DEEPLY PHENOTYPED OF A FEW HUNDRED CAN START TO. THE RARE VARIANT STUFF, NOT SO WELL, BUT A POLYGENIC SCORE EFFECT, POTENTIALLY DOABLE.

BEN, YOU WANTED TO ADD SOMETHING TO THAT.

DR. NEALE: YEAH. I THINK I MIGHT TAKE A SUBTLY DIFFERENT TACK. AND I BROADLY AGREE WITH WHAT JONATHAN WAS SAYING, BUT I THINK THERE ARE A FEW OTHER PIECES TO PUT ON THE TABLE.

SO THE LINE OF EVIDENCE THAT SAYS THAT THE COMMON VARIANTS AND THE RARE VARIANTS ARE MAYBE CONVERGING ON SIMILAR BIOLOGY, I THINK, IS ACTUALLY A VERY IMPORTANT ONE. BECAUSE YOU COULD -- BECAUSE THERE ARE OPEN QUESTIONS ABOUT WHAT IS THE CELLULAR READOUT THAT IS RELEVANT? WHAT IS THE RIGHT PROCESS TO MODEL IN AN IPS NEURONAL LINE, AND HOW ACCURATE DOES THAT IPS NEURONAL LINE HAVE TO BE TO RECAPITULATE THE SORT OF UNDERLYING PHYSIOLOGICAL PROCESS THAT WE ARE TRYING TO UNDERSTAND? AND WHAT DO YOU NEED TO ALSO CO-CULTURE IT WITH? HOW COMPLICATED DOES IT NEED TO BE? DOES IT NEED TO BE THE FULL ORGANOID, ET CETERA?

AND I THINK ALL OF THESE QUESTIONS ARE STILL VERY MUCH OPEN QUESTIONS IN THE FIELD. BUT I WOULD FLAG THAT THE RARE VARIANTS OF LARGE EFFECT ON RISK PROVIDE AN OPPORTUNITY TO SORT OF MAYBE GET A VERY FAST READOUT ON SOME OF THESE ASSAYS OR AT LEAST DISPATCH CERTAIN ASSAYS AS NOT SHOWING ANYTHING IN THE CONTEXT OF THE RARE VARIANT, YES, NO, ET CETERA, ET CETERA. BUT BECAUSE WE ARE SEEING CONVERGENCE BETWEEN THE COMMON GENETIC RISK AND THE RARE GENETIC RISK, IT SEEMS LIKE A NATURAL OPPORTUNITY FOR STAGING WHERE YOU USE YOUR RARE VARIANTS AS AN INITIAL PROBE, IDENTIFY WHAT READOUTS ARE RELEVANT OR SHOW PERTURBATION IN THAT, AND THEN SCALE UP THE NUMBER OF LINES SO THAT YOU CAN TEST WHETHER COMMON GENETIC VARIANTS THAT ARE ASSOCIATED WITH THE DISORDER UNDER STUDY ARE ALSO SHOWING CONSISTENT DOSE RESPONSE ON THE FUNCTIONAL READOUT THAT YOU'RE DOING.

BECAUSE I THINK IT'S EASY TO GET TO, LIKE, THIS IS DIFFERENT BECAUSE WE KNOCKED OUT A GENE, BUT IS IT ACTUALLY REALLY RELEVANT TO THE CORE PATHOGENESIS OF THE ILLNESS? IT'S A LOT HARDER TO GET TO DOING THAT IN MORE LINES AFTER YOU'VE ESTABLISHED YOUR ASSAY IS HIGH CONFIDENCE.

AND THEN THE FINAL THING I WOULD ADD IN

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TERMS OF NUANCE TO JONATHAN'S PROPOSAL ABOUT TAKING HIGH PRS AND LOW PRS IS WHEN THOSE IDEAS ARE FLOATED AROUND THESE PARTS, I SAY QUITE STRONGLY THAT WE NEED TO INCLUDE MIDDLE PRS AS WELL BECAUSE TWO GROUP COMPARISONS, YOU CAN FOOL YOURSELF, BUT IT'S A LOT HARDER TO FOOL YOURSELF WITH LOW, MEDIUM, HIGH THAN IT IS TO FOOL YOURSELF WITH TWO GROUPS AND THEN THIS IS LOW AND THIS IS HIGH.

DR. SEBAT: YOU'RE PREACHING TO THE CHOIR. GAIN-OF-FUNCTION, LOSS-OF-FUNCTION, AND NO FUNCTION.

JONATHAN HAS A QUESTION.

CHAIRMAN GOLDSTEIN: J.T.

CHAIRMAN THOMAS: SO I HAVE A DRUG DEVELOPMENT QUESTION I'M JUST CURIOUS ABOUT. SO NORMALLY IN DRUG DEVELOPMENT, ONE HAS ESTABLISHED A TARGET AND YOU DEVELOP A DRUG FOR WHICH THERE'S A DEFINABLE MECHANISM OF ACTION WITH THE TARGET, AND YOU CAN HAVE MEASURABLE RESULTS OF HIGH THROUGHPUT SCREENING OR WHATEVER, AND YOU SETTLE UPON SOMETHING THAT IS A THERAPEUTIC CANDIDATE AND YOU WORK IT THROUGH THE TRIAL PROCESS AND ULTIMATELY, HOPEFULLY, YOU COME UP WITH SOMETHING THAT'S COMMERCIALIZABLE.

HOW ARE -- AND I PROFESS TO NOT HAVE ANY HANDLE ON WHAT DRUGS ARE OUT THERE AT THE MOMENT THAT HAVE AN IMPACT ON SCHIZOPHRENIA OR BIPOLAR OR

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WHATEVER. BUT TO THE EXTENT THOSE DRUGS ARE OUT THERE, HOW WERE THEY DEVELOPED WHEN THERE'S NO -- THE FIELD OF GENETIC AND GENOMIC ANALYSIS OF THE UNDERLYING DISEASE IS IN ITS RELATIVE INFANCY AND THERE'S NOT AN ESTABLISHED LIST OF TARGETS TO GO AFTER AND, THEREFORE, NO WAY OF REALLY UNDERSTANDING THE MECHANISM OF ACTION OF A DRUG THAT THEY ARE DEVELOPING.

HOW ARE THOSE DRUGS, HOW HAVE THEY BEEN DEVELOPED TO THIS POINT WHEN THE UNDERLYING KNOWLEDGE THAT WOULD BEST INFORM THEM ISN'T RIPE ENOUGH AT THIS STAGE?

DR. SEBAT: LET ME -- JUST SO I CAN CONJURE UP AN INTERPRETABLE ANSWER, I'LL TRY TO REPHRASE OR REFRAME THAT JUST A LITTLE BIT. SO THE PROBLEM REALLY IS WE NEED THERAPEUTIC TARGETS. WE ARE STARTING WITH A LIST OF GENES. AND HOW DO WE GO FROM A LIST OF GENES TO THERAPEUTIC TARGETS? AND I THINK THAT, OBVIOUSLY, THE ACTUAL EFFECTS OF GENES ON CIRCUITS IS A TRACTABLE PROBLEM. UNDERSTANDING THAT IS DOABLE.

UNDERSTANDING THE EFFECTS OF DRUGS ON PATHWAYS AND CIRCUITS IS ALSO DOABLE BY USING EXACTLY THE SAME SYSTEMS, IF YOU USE IPS CELLS TO MEASURE THE EFFECTS OF DRUGS.

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AND SO WHAT SOME PEOPLE ARE STARTING TO THINK ABOUT IS KIND OF A SPECTRUM OF PHARMA, A SPECTRUM OF DRUGS AND THEIR EFFECTS AND THE GENETIC EFFECTS AND TRYING TO BE ABLE TO MATCH THE DRUG WITH THE GENE BASED ON WHAT YOU KNOW ABOUT THE GENETIC EFFECTS IS ARE THERE DRUGS THAT ARE ACTUALLY REVERSING WHAT YOU SEE?

AND, OF COURSE, THE GENETIC TOOLS, CRISPR ACTIVATION, CRISPR INHIBITION, AND OTHER TYPES OF TOOLS ARE ALSO THERE TO SEE IF YOU CAN RESCUE THE PHENOTYPES. SO YOU HAVE THE MAIN EFFECTS OF THE GENES, YOU HAVE GENETIC TOOLS THAT WILL TELL YOU CAN THIS BE RESCUED, AND THEN, OF COURSE, YOU WILL HAVE -- AND THAT IN OF ITSELF MAKES SOMETHING A TARGET.

THE QUESTION IS WILL THERE BE A SMALL MOLECULE THAT MIGHT WORK TOWARDS THAT? THAT'S ANOTHER QUESTION. OR ARE THERE OTHER SMALL MOLECULES THAT RECAPITULATE THAT EFFECT? THAT'S KIND OF HOW I WOULD THINK OF IT AS REALLY TRYING TO UNDERSTAND THE EFFECTS OF GENES, UNDERSTANDING IF IT'S REVERSIBLE, AND THEN UNDERSTANDING WHETHER THERE ARE SMALL MOLECULES THAT WILL DO THE SAME THING.

DR. NEALE: SO TO ANSWER YOUR QUESTION,

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J.T., ABOUT WHAT IN THE MEDICINE CABINET EXISTS ALREADY AND HOW WE GOT HERE, PRETTY MUCH EVERY DISCOVERY WAS SERENDIPITOUS. SO LITHIUM WAS FOUND BY SOME WORK ON GUINEA PIGS AND SHOWING THAT THE GUINEA PIGS APPEARED MORE RESTFUL. AND THEN THIS WAS DONE IN THE LIKE LATE '40S, EARLY '50S, AND THEN PUSHED INTO HUMANS TO SEE IF THAT WOULD MAKE THEM CALM DOWN. AND IT HAD CALMING EFFECTS, BUT THERE WAS TOXICITY TO DEAL WITH.

I THINK THE ANTIPSYCHOTICS WERE DEVELOPED PRIMARILY AS ANESTHETIC AGENTS AND THEN SHOWN SERENDIPITOUSLY TO HAVE THESE OTHER SIDE EFFECTS.

SO LITERALLY BASICALLY EVERY DRUG THAT IS OUT THERE HAS BEEN FOUND NOT THROUGH A RATIONAL BASED FOUNDATIONAL HERE IS AN INSIGHT. THIS IS AN UNDERSTANDING OF PATHOGENIC MECHANISM. LET US GO OUT AND TREAT IT, WHICH IS WHAT JONATHAN WAS TRYING TO, I THINK, TELL US OF WHERE WE MIGHT GO. IT WAS MORE LIKE PEOPLE ARE MUCKING AROUND WITH MEDICINAL CHEMISTRY, FOUND SOME INTERESTING COMPOUNDS OR SUBSTANCES, GAVE THEM TO MODEL ORGANISMS, READ OUT SOME BEHAVIORAL CONSEQUENCES, AND THEN SAID, WELL, LET'S TRY IT IN HUMANS AND SEE WHAT HAPPENS.

DR. LEVITT: AND IN SOME WAYS IT'S EVEN MORE SERENDIPITOUS BECAUSE SOMETIMES IT WAS A SIDE

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EFFECT LIKE ANTIHISTAMINES WERE USED IN HOSPITALS, PSYCHIATRIC HOSPITALS, IN LONG ISLAND WHERE INDIVIDUAL SCHIZOPHRENIA AND THE SIDE EFFECT OF GIVING THEM AN ANTIHISTAMINE THAT WAS DEVELOPED IN THE 1940S WAS THAT IT CALMED THEIR PSYCHOSIS THROUGH A STRIATAL RECEPTOR.

THERE'S A REALLY GOOD BOOK THAT I THINK IS A GOOD BOOK CALLED *BETTER THAN PROZAC*, WHICH IS WRITTEN BY THE FORMER CHAIR OF PSYCHIATRY AT UCSF SOME OF YOU MAY KNOW, SAM BARONDES. AND IT'S AN INTERESTING READ TO SORT OF GET AT THE HISTORY THAT BEN JUST REFERENCED WHERE MOST OF WHAT WE HAVE, ALMOST ALL OF WHAT WE HAVE IS PURE COINCIDENCE OR LUCK OR SOME OBSERVATION THAT SOMEBODY MADE THAT HAD NOTHING TO DO WITH TARGETING.

CHAIRMAN GOLDSTEIN: GREAT. INTERESTING. ROSA.

DR. CANET-AVILES: THANK YOU, DR. GOLDSTEIN. I JUST WANTED TO PROVIDE A LITTLE BIT MORE INFORMATION WITH REGARDS TO HOW CAN WE MODEL THESE IN IPS CELL LINES AND THE MENTION ABOUT HIGH POLYGENIC RISK SCORES AND LOW POLYGENIC RISK SCORES. IN FACT, I JUST WANTED OUR BOARD TO KNOW THAT THERE'S ACTUALLY A PAPER FROM KRISTIN BRENNAND'S LAB IN A COLLABORATION THAT SHOWED THAT OUR OWN

CIRM-FUNDED HUMAN PLURIPOTENT STEM CELL LINES ARE AVAILABLE TO ALL RESEARCHERS.

THEY DID A STUDY OF 12 IPS CELL LINES FROM CONTROL DONORS THAT THEY HAD EXTREME EITHER LOW OR HIGH POLYGENIC RISK SCORES. AND THREE INDEPENDENT LABS VALIDATED THE SUITABILITY OF THOSE LINES FOR CRISPR-BASED IATROGENIC COMPARISONS OF NEURONS AND GLIA OR OTHER.

SO I JUST WANTED TO LET YOU KNOW THAT THIS IS AVAILABLE, AND IT'S KIND OF A PROOF OF PRINCIPLE AND A VERY GOOD, NICE VALIDATION BY THREE DIFFERENT LABS THAT THAT EXISTED.

DR. SEBAT: I THINK A POWER CALCULATION WOULD TELL YOU THAT STUDIES -- IF YOU DO A LOT OF STUDIES OF 12 VERSUS 12, YOUR LITERATURE IS GOING TO BE REALLY DIFFICULT TO UNDERSTAND.

DR. CANET-AVILES: WELL, THAT'S A -- IT'S A START.

DR. SEBAT: YEAH, THAT'S THE PROBLEM. AND THAT'S A GREAT PROOF OF PRINCIPLE. BUT IF YOU WERE GOING TO THEN MAKE THAT A RESOURCE AND HAVE A DOZEN DIFFERENT LABS DO IT AND YOU WANT INTERPRETABLE RESULTS, YOU JUST HAVE TO DO THE BASIC POWER CALCULATIONS. AND 12 VERSUS 12 IS NOT GOING TO GIVE YOU WHAT YOU NEED.

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CHAIRMAN GOLDSTEIN: SO, ROSA, COULD YOU POST A COUPLE OF THOSE REFERENCES?

DR. CANET-AVILES: ABSOLUTELY. YES. I'LL PASS THEM ON.

CHAIRMAN GOLDSTEIN: YEAH. GREAT. THANK YOU.

WHO IS (310) 922 WHATEVER OVER HERE?

MS. DEQUINA-VILLABLANCA: THAT WOULD BE A PUBLIC COMMENT, LARRY.

CHAIRMAN GOLDSTEIN: PUBLIC COMMENT. OKAY. WE ARE NOT QUITE THERE, BUT WE'RE GOING TO GET THERE MOMENTARILY.

SO ANY FINAL QUESTIONS FOR DRS. NEALE OR SEBAT BEFORE WE MOVE IN THE DIRECTION OF PUBLIC COMMENT? OKAY.

SO LET ME GIVE US A TRANSITION. SO OUR NEXT COUPLE OF MEETINGS WILL MOVE IN AND BEGIN TO FOCUS ON CELLULAR MISBEHAVIOR AND ODD BEHAVIOR AT THE LEVEL OF IPS-DERIVED NEURONS AND, OF COURSE, GLIA, WHICH WE REALLY SHOULD NOT FORGET. ONE OF THE PUBLIC COMMENTS MAY CONCERN GLIA, IN FACT. BUT THEY'RE IMMENSELY INTERESTING CELLS AND MAY HAVE A GREAT DEAL OF EFFECT ON THE BEHAVIOR OF NEURONS IN WAYS THAT I'D SAY WE STILL HAVE VERY INADEQUATE UNDERSTANDING.

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SO WE'LL BEGIN TO WORK OUR WAY IN THAT DIRECTION AS WELL AS CONTINUING TO DISCUSS CONCEPT PLANS AND WHERE WE MIGHT WANT TO THINK ABOUT TARGETING FUNDING.

SO IF THERE'S NOTHING ELSE FROM THE TASK FORCE, THEN, MARIANNE, CAN WE MOVE TO PUBLIC COMMENT?

MS. DEQUINA-VILLABLANCA: YES, WE CAN. AND EACH PUBLIC COMMENT IS FOR THREE MINUTES. WE'VE GOT (310) 592-2960. IF YOU CAN UNMUTE YOURSELF.

CHAIRMAN GOLDSTEIN: AND IDENTIFY YOURSELF PLEASE. PHONE NUMBER ENDING IN 960, ARE YOU GOING TO UNMUTE YOURSELF?

DR. GESCHWIND: IT'S DAN GESCHWIND FROM UCLA. I JUST FIGURED OUT HOW TO UNMUTE MYSELF. I REALLY APOLOGIZE.

CHAIRMAN GOLDSTEIN: THANKS, DAN.

DR. GESCHWIND: SO REALLY I WANT TO THANK YOU FOR THIS OPPORTUNITY AND FOR THE REALLY COMPREHENSIVE AND INSIGHTFUL PRESENTATIONS AND THE DISCUSSION AROUND IT FROM BOTH DRS. NEALE AND SEBAT. I THINK THEY EMPHASIZED HOW GENETICS HAS BEEN REMARKABLY SUCCESSFUL IN ACTUALLY IDENTIFYING FACTORS THAT CAUSE NEUROPSYCHIATRIC DISEASE FROM SCHIZOPHRENIA AND BIPOLAR TO ASD AND

NEURODEVELOPMENTAL DISORDERS. AND, OF COURSE, BOTH OF THEM HAVE PLAYED LEADING ROLES IN THAT WORK AS THEY DESCRIBED AND CONTINUE TO DO SO. SO THAT WAS A REALLY FANTASTIC PRESENTATION.

I JUST WANT TO EMPHASIZE TWO THINGS THAT THEY SAID. THE RARE VARIANTS IMPLICATE SPECIFIC GENES, LOSS-OF-FUNCTION IN MANY CASES. THERE'S STILL A TON TO LEARN. BUT MOST GENETIC VARIATION LIES IN NONPROTEIN CODING REGIONS OF THE GENES, THAT THESE REGIONS DON'T ACTUALLY CODE TO PROTEINS. IT'S HARD TO KNOW LOSS- VERSUS GAIN-OF-FUNCTION. AND THESE REGIONS ARE THOUGHT AND MANY KNOWN TO REGULATE GENE EXPRESSION IN SOME WAY OR ANOTHER EITHER BY TRANSCRIPT LEVEL OR BY SLICING. AND SO, THEREFORE, UNDERSTANDING THE REGULATION OF GENE EXPRESSION AND FUNCTION IS A KEY ELEMENT.

ONE OF THE CONSORTIA THAT I THINK CIRM HAS AN OPPORTUNITY TO REALLY INTERACT WITH IS NOT ONLY THE BRAIN CONSORTIUM, BUT THE PSYCHENCODE CONSORTIUM, WHICH WAS INITIATED BY NIMH TO DEVELOP AN UNDERSTANDING OF GENE REGULATION IN THE BRAIN BECAUSE GENE REGULATION IS SO TISSUE AND DEVELOPMENTAL STAGE SPECIFIC.

SO WHILE CODING REGIONS THAT CODE FOR PROTEINS ARE HIGHLY CONSERVED EVEN ACROSS VERTEBRATE

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ALL THE WAY TO MOUSE AND ZEBRAFISH AND, THEREFORE, MAKING ANIMAL MODELS IS A VERY REASONABLE AND POWERFUL APPROACH. THE NONCODING REGIONS THAT WE ARE TALKING ABOUT IN WHICH MOST DISEASE ASSOCIATED GENETIC VARIATION LIES ARE NOT THAT WELL CONSERVED ACROSS SPECIES OR THEIR CONSERVATION IS POORLY UNDERSTOOD. AND, THEREFORE, HAVING MODELS WITH HUMAN GENETIC BACKGROUNDS IS NECESSARY. AND THIS NECESSITATES RIGHT NOW THE USE OF HUMAN-DERIVED MODELS THAT CAN REPRESENT HUMAN GENETIC DIVERSITY AND GENETIC RISK IN REGULATORY NETWORKS.

SO THIS PROVIDES AN ENORMOUS OPPORTUNITY FOR CIRM IN CALIFORNIA. THE QUESTION IS HOW VALID ARE IPSC MODELS? BEN ADDRESSED SOME OF THAT. THERE'S BEEN QUITE A BIT OF WORK THAT WE COULD MAYBE DISCUSS IN FUTURE MEETINGS AROUND THIS. THE MACOSKO LAB, CARLOTTO LAB, BRENNAND LAB AND OTHERS, TEMPLE LAB, HAVE USED GENOMIC METHODS TRANSCRIPTOMIC EPIGENETIC MARKS TO SHOW THAT IPSC-DERIVED NEURONAL LINES AND GLIA LINES MODELS HUMAN NEURODEVELOPMENT WITH RELATIVELY HIGH FIDELITY. THAT IS, THE EARLY STAGES OF DEVELOPMENT. AND SO THEY REALLY PROVIDE THIS ENORMOUS OPPORTUNITY.

I THINK JON THOMAS MENTIONED HOW CLOSE ARE WE TO THERAPIES. I MEAN THE HUNDREDS OF IDENTIFIED

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GENETIC RISK FACTORS PROVIDE AN UNBELIEVABLE OPPORTUNITY FOR DIRECTED DEVELOPMENT OF THERAPEUTICS. BUT TO DO THIS, YOU CAN'T STUDY ONE --

MS. DEQUINA-VILLABLANCA: YOUR THREE MINUTES ARE UP.

DR. GESCHWIND: OKAY. TEN SECONDS.

HIGH THROUGHPUT IN VITRO MODELS ARE NEEDED FOR THIS. SO THE IPSC MODELS FROM HUMAN CELLS PROVIDE A UNIQUE OPPORTUNITY FOR THESE HIGH THROUGHPUT STUDIES. SO I JUST WANTED TO REALLY EMPHASIZE THAT. IT'S A GREAT OPPORTUNITY FOR CIRM, AND I'M SO GLAD THAT WE ARE FOCUSING ON THIS NOW. THANK YOU.

CHAIRMAN GOLDSTEIN: THANK YOU VERY MUCH, DAN. OKAY. NEXT UP IS --

MS. DEQUINA-VILLABLANCA: 310 (UNINTELLIGIBLE). IF YOU COULD PRESS 9 TO UNMUTE.

DR. BUTLER: THAT'S ACTUALLY MY PHONE NUMBER, MY OFFICE PHONE NUMBER. SO IT WAS VERY CONFUSING AS TO HOW THIS WAS GOING TO WORK.

SO MY NAME IS SAMANTHA BUTLER, AND I'M A PROFESSOR IN THE NEUROBIOLOGY DEPARTMENT AT THE DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA WHERE I HOLD THE ELEANOR LESLIE CHAIR IN PIONEERING BRAIN

RESEARCH. AND MY STUDIES FOCUS ON THE DEVELOPMENT AND REGENERATION OF SENSORY RELAY CIRCUITS IN THE SPINAL CORD. SO I'D LIKE TO MAKE THE FOLLOWING POINTS TO CONSIDER ABOUT HOW CIRM ALLOCATES THIS 1.5 BILLION IN NEUROSCIENCE FUNDING.

SO, FIRST, GIVEN THAT MANY NEUROLOGICAL DISEASES AND SYNDROMES HAVE THEIR BASIS IN EARLY DEVELOPMENT, IT IS ESSENTIAL TO FUND BASIC SCIENCE AND THE MECHANISMS BY WHICH THESE NEURAL CIRCUITS FIRST FORM IN THE BRAIN AND SPINAL CORD. GIVEN THE FEDERAL REGULATIONS ON HUMAN EMBRYONIC AND STEM CELL RESEARCH, FUNDING FROM CIRM IS CRITICAL FOR MAKING ANY HEADWAY IN UNDERSTANDING WHAT POTENTIALLY HUMAN SPECIFIC MECHANISMS THAT UNDERPIN OUR ABILITY TO THINK, MOVE, AND FEEL.

SO SECOND, THIS RESEARCH NEEDS INSIGHT FROM BOTH STEM CELL AND NEUROBIOLOGISTS. THE NEUROSCIENTIST'S PERSPECTIVE HAS TOO OFTEN BEEN MISSING AND IS URGENTLY NEEDED TO IMPROVE RIGOR. IT'S NOT ENOUGH TO MAKE GENERIC EYE NEURONS FOR CELLULAR REPLACEMENT STUDIES, FOR EXAMPLE, WITHOUT THE NECESSARY KNOWLEDGE OF THE TYPE AND FUNCTION OF THE NEURON BEING REPLACED. THESE STUDIES ARE LIKELY TO FAIL WITHOUT THAT KNOWLEDGE.

SO THIRD AND FINALLY, PLEASE, PLEASE

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CONSIDER FUNDING A MECHANISM THAT INVESTS IN HIGH RISK, HIGH REWARD STUDIES ON BASIC NEUROLOGICAL MECHANISMS PERHAPS EVEN IN MODEL SYSTEMS. THE COSTS ARE VERY SIGNIFICANTLY LESS THAN FUNDING TRANSLATIONAL CLINICAL WORK AND LARGE-SCALE GENETIC SURVEY STUDIES, FOR EXAMPLE. AND THESE ARE THE STUDIES THAT HAVE HISTORICALLY GENERATED THE MOST SURPRISING AND IMPORTANT BREAKTHROUGHS IN OUR SCIENTIFIC UNDERSTANDING. NO ONE CAN PREDICT WHEN AND WHERE THESE BREAKTHROUGHS WILL COME FROM, BUT IT'S CRITICAL TO KEEP THIS PIPELINE OF RESEARCH ALIVE AND VIBRANT. THANK YOU SO MUCH.

CHAIRMAN GOLDSTEIN: THANK YOU, DR. BUTLER. VERY THOUGHTFUL AND PITHY.

LET'S SEE. NEXT UP. BEN NOVITCH.

DR. NOVITCH: HI. AND THANKS FOR THE OPPORTUNITY TO SHARE MY THOUGHTS. SO MY NAME IS BEN NOVITCH. I'M A PROFESSOR AT UCLA AND A MEMBER OF OUR BROAD STEM CELL RESEARCH CENTER.

I'M SO EXCITED TO HEAR THE PRESENTATIONS TODAY REALLY GIVING SOME FOCUS TO MENTAL HEALTH DISORDERS AS SOMETHING THAT CIRM SHOULD GO AFTER. AND WE KNOW THAT THE SCOPE IS AFFECTING MILLIONS OF PEOPLE IN CALIFORNIA AND HALF A BILLION PEOPLE ACROSS THE WORLD. AND WE KNOW VERY LITTLE ABOUT HOW

TO TREAT THESE DISORDERS.

AND SO OUR ABILITY TO DEVELOP EFFECTIVE THERAPY REALLY DEPENDS UPON OUR GETTING A BETTER UNDERSTANDING OF THE INNER WORKINGS OF THE HUMAN BRAIN AND THE PATH OF PHYSIOLOGICAL MECHANISMS BEHIND THESE DISORDERS. THERE'S MANY QUESTIONS THAT WE REALLY DON'T KNOW THE ANSWERS TO, INCLUDING WHEN, WHERE, AND HOW DO MENTAL ILLNESSES BEGIN.

AND SO I JUST WANTED TO POINT OUT BY REITERATING MY COLLEAGUE DR. BUTLER, THAT THE CENTRAL NERVOUS SYSTEM IS ONE OF THE FIRST STRUCTURES TO BE FORMED DURING A REGENESIS, AND A LOT OF WHAT GOES WRONG CAN BE TRACED BACK TO DEVIATIONS IN NORMAL DEVELOPMENT THAT CAN RESULT IN NEUROLOGICAL DISORDERS THAT MANIFEST EARLY IN LIFE, SUCH AS EPILEPSY AND AUTISM, BUT ALSO AT LATER TIMES, SUCH AS SCHIZOPHRENIA. AND THE RECENT STUDIES HAVE EVEN SHOWN THAT DISORDERS THAT WE TRADITIONALLY VIEW AS ADULT ONSET, SUCH AS MOOD DISORDERS AND NEURODEGENERATION, NEURODEGENERATIVE CONDITIONS, CAN EMERGE AS A CONSEQUENCE OF VULNERABILITIES THAT ARE CONVEYED EARLY IN LIFE.

AND MANY DISORDERS ARISE FROM GENETIC VARIATIONS AS WE HEARD SO ELEGANTLY ABOUT TODAY AND HOW THESE CAN AFFECT, IMPACT THE ASSEMBLY OR THE

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FUNCTION OF NEURAL CIRCUITS FROM THE OUTSET OR POTENTIALLY TO RAISE -- TO REVEAL THEMSELVES WHEN COMBINED WITH ENVIRONMENTAL TRIGGERS SUCH AS TOXINS, PATHOGENS, STRESS, AND TRAUMA. AND THIS IS SOMETHING THAT WE HAVE REALLY VERY LITTLE UNDERSTANDING OF AND SOMETHING THAT I THINK WE NEED TO THINK ABOUT IN THE FUTURE IN TERMS OF GENE ENVIRONMENT INTERACTIONS.

AND SO TO MEET THESE CHALLENGES, I THINK THAT I WOULD LIKE TO URGE CIRM TO INCREASE SUPPORT FOR THE FOLLOWING AREAS OF RESEARCH IN THE NEUROSCIENCE PORTFOLIO, LEVERAGING ALL THE ADVANCES WE'VE HEARD ABOUT WITH GENOMICS AS WELL AS DIRECTED DIFFERENTIATIONS OF IPS CELLS AND ESTABLISHMENT OF ORGANOID MODELS.

SO FIRST OF ALL, I THINK WE NEED TO SPEND MORE WITH CHARACTERIZING THE BASIC MECHANISMS AND UNIQUE FEATURES OF HUMAN DEVELOPMENT AND MATURATION ACROSS THE LIFE SPAN.

I THINK SECOND, WE NEED TO DEFINE CELLULAR AND INTRINSIC -- SORRY -- INTRINSIC AND ENVIRONMENTAL INFLUENCE THAT GOVERN HEALTHY AND MALADAPTIVE BRAIN DEVELOPMENT.

AND THIRD, WE NEED TO REALLY EXPAND THE PIPELINE FOR CREATING MODELS FOR HUMAN

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NEURODEVELOPMENTAL AND NEUROPSYCHIATRIC DISEASES SO THAT WE CAN IMPROVE OUR THERAPEUTIC DEVELOPMENT PIPELINE AS WELL.

AS I THINK WE'VE HEARD ABOUT, WE HAVE A FEW IPS MODELS FOR A FEW DISORDERS. WE NEED TO MAKE THAT MANY MORE TO GET THE BREADTH OF THE HUMAN POPULATION IN THESE MODELS.

THANKS FOR YOUR ATTENTION.

CHAIRMAN GOLDSTEIN: THANK YOU VERY MUCH, DR. NOVITCH.

LARRY ZIPURSKY, YOU'RE UP.

DR. ZIPURSKY: I'M A PROFESSOR OF BIOLOGICAL CHEMISTRY AT THE DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA. I SERVE AS CHAIR OF THE UCLA NEUROSCIENCE THEME, WHICH PROMOTES INTERDISCIPLINARY EFFORTS IN NEUROSCIENCE ACROSS CAMPUS AND BASIC TO TRANSLATIONAL NEUROSCIENCE. AND I'M HERE TODAY TO ENCOURAGE CIRM TO APPLY THE $1.5 BILLION COMMITTED TO ADDRESSING THE CHALLENGE OF MENTAL ILLNESS IN CREATIVE AND IMPACTFUL WAYS TO REDUCE THE BURDEN OF NEUROPSYCHIATRIC DISORDERS ON PATIENTS, FAMILIES, AND OUR COMMUNITIES.

THE BRAIN IS THE MOST COMPLICATED ORGAN, AND IT IS THIS COMPLEXITY THAT PRESENTS ENORMOUS CHALLENGES TO UNDERSTANDING THE CAUSES OF MENTAL

ILLNESS AND THE DEVELOPMENT OF THERAPIES FOR EFFECTIVELY TREATING THEM. OUR BRAINS AND, INDEED, WHO WE ARE REFLECT THE INTERACTIONS BETWEEN NATURE, THE GENES WE INHERITED FROM OUR PARENTS, AND NURTURE THE POWERFUL INFLUENCE OF THE ENVIRONMENT ON THE DEVELOPMENT OF A CHILD'S BRAIN.

IT IS WELL DOCUMENTED THAT BOTH GENES AND ADVERSE CHILDHOOD EXPERIENCES FROM FOOD INSECURITY TO VIOLENCE IN OUR COMMUNITIES ARE MAJOR DETERMINANTS OF MENTAL ILLNESS, NOT ONLY IN CHILDREN, BUT PERSISTING THROUGHOUT ADULT LIFE.

PROGRESS IN UNDERSTANDING MENTAL ILLNESS REQUIRES AN UNDERSTANDING OF HOW OUR CHILDREN'S BRAINS DEVELOP. WHILE CONSIDERABLE PUBLIC AND PRIVATE FUNDING HAS BEEN DEVOTED TO NEURODEGENERATIVE DISORDERS AND UNDERSTANDING HOW THE ADULT BRAIN WORKS, RESEARCH INTO HOW THE BRAIN DEVELOPS AND THE ROLE OF GENES AND THE ENVIRONMENT IN THIS PROCESS HAS BEEN BY COMPARISON POORLY FUNDED. CIRM CAN FILL THIS VOID BY DEVELOPING CREATIVE AND IMPACTFUL DISCOVERY, SCIENCE-BASED INITIATIVES TO UNDERSTAND HOW THE HUMAN BRAIN DEVELOPS. THIS WILL PROVIDE FOUNDATIONAL KNOWLEDGE TO ADDRESS THE ROOT CAUSES OF MENTAL ILLNESS. THIS IS AN ESSENTIAL STEP WITH USING STEM CELLS AND

ORGANOID-BASED TECHNOLOGIES TO CREATE APPROPRIATE MODELS FOR UNDERSTANDING BRAIN DISORDERS AND FOR USING THESE IN CREATIVE WAYS TO DEVELOP THERAPEUTICS.

SO WHAT'S THE BEST WAY FORWARD TO ACCOMPLISH THIS? I URGE CIRM TO CREATE COMPETITIVE INITIATIVES IN DISCOVERY NEUROSCIENCE TO CHALLENGE THE EXTRAORDINARY SCIENTISTS AT THE MANY SUPERB PUBLIC AND PRIVATE INSTITUTIONS IN CALIFORNIA TO PROPOSE AMBITIOUS, CREATIVE, AND TRANSFORMATIONAL RESEARCH PROGRAMS TO UNDERSTAND HOW THE HUMAN BRAIN DEVELOPS. AREAS OF FOCUS SHOULD NOT BE PROSCRIPTIVE. IT SHOULD TAKE ADVANTAGE OF THE BREADTH OF SCIENTIFIC EXPERTISE AND RESEARCH EXCELLENCE AT OUR CALIFORNIA INSTITUTIONS.

INDEED, A BROAD INITIATIVE BRINGING TOGETHER GENETICISTS, BIOCHEMISTS, CELL AND DEVELOPMENTAL BIOLOGISTS, AND NEUROSCIENTISTS TO TACKLE THE MECHANISTIC BASIS OF BRAIN DEVELOPMENT WOULD BE A BOLD, TRANSFORMATIONAL STEP IN CONFRONTING THE CHALLENGES OF MENTAL ILLNESS. THANK YOU.

CHAIRMAN GOLDSTEIN: THANK YOU, LARRY. VERY THOUGHTFUL.

I'LL JUST POINT OUTRIGHT NOW, TAKING

CHAIR'S PREROGATIVE, THAT THE CONCEPT PLAN THAT ROSA DESCRIBED IS ACTUALLY A GREAT WAY TO START DELVING INTO THOSE AREAS BECAUSE IT'S DESIGNED TO GET MULTIDISCIPLINARY TEAMS TOGETHER.

NEXT, DR. CHEN.

DR. CHEN: HI. I'M PATRICK CHEN. AND I'M ADJUNCT ASSISTANT PROFESSOR AT UCLA, THE DEPARTMENT OF PSYCHIATRY. AND I WORK ON KIND OF UNDERSTANDING THE MECHANISMS BY WHICH GENETIC VARIATION LEADS TO BEHAVIORAL VARIATION. I MEAN I DON'T HAVE AS MUCH TO ADD. I THINK EVERYONE, ALL OF MY COLLEAGUES, HAVE SAID A LOT MORE ELOQUENTLY THAN I CAN SAY. BUT I JUST WANTED TO EMPHASIZE THAT I THINK IT'S, TO ME AT LEAST, IT SEEMS IMPORTANT THAT WE SHOULD REALLY WORK TO KIND OF JOIN THE GREAT LABS AND CAMPUSES IN BOTH GENETICS AND IN NEUROSCIENCE ACROSS CALIFORNIA AND ENCOURAGE THAT SORT OF COLLABORATION THAT LARRY JUST MENTIONED.

I THINK THAT IT'S REALLY IMPORTANT THAT WE IN INVEST IN NEW STRATEGIES TO TURN GENETIC DISCOVERIES INTO UNDERSTANDING OF MECHANISM, AND SPECIFICALLY NEUROMECHANISMS.

I THINK WE NEED NEW APPROACHES TO LEARN HOW THE GENES WILL BE IDENTIFIED, CONTRIBUTE TO THE RISK OF MENTAL ILLNESSES, AND THAT CAN ONLY REALLY

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BE ACCOMPLISHED BY REALLY MARRYING THE FIELDS OF GENETICS AND NEUROSCIENCE. AND I THINK, FROM MY PERSPECTIVE, WE ALSO SHOULDN'T REALLY FORGET THAT BEHAVIOR IS A REALLY IMPORTANT COMPONENT OF THIS. AND REALLY UNDERSTANDING HOW DO WE GET FROM SEQUENCE ARE VARIANTS, DNA SEQUENCE VARIANTS TO BEHAVIORAL VARIATION AND ALL THE LAYERS IN BETWEEN, I FEEL LIKE THERE REALLY SHOULD BE A FOCUS ON UNDERSTANDING THINGS. AND ONE OF THESE NEW APPROACHES THAT HASN'T REALLY BEEN EXPLORED AS MUCH AS IT COULD BE IS REALLY TAKING FROM A BEHAVIOR PERSPECTIVE AND WORKING FROM THERE.

AND I THINK REALLY JUST EMPHASIZING THAT WE DO NEED AN EFFICIENT, COLLABORATIVE APPROACH BETWEEN THE GENETICISTS AND NEUROSCIENTISTS AND EVERYTHING IN BETWEEN WOULD BE REALLY USEFUL. THANK YOU.

CHAIRMAN GOLDSTEIN: TERRIFIC. THANK YOU, DR. CHEN.

JONATHAN, SHORT PLEASE, BECAUSE WE ARE RIGHT UP AGAINST THE END TIME.

DR. SEBAT: I DON'T WANT TO TAKE ANY TIME AWAY FROM PUBLIC COMMENT. I JUST WANTED -- PATRICK DEFINITELY HIGHLIGHTS AN IMPORTANT POINT, WHICH IS THAT THE BEHAVIOR AND COGNITION ELEMENTS WOULD BE

REALLY VALUABLE TO HAVE. IF YOU'RE DOING -- IF YOU'RE MAKING HUMAN-DERIVED MODELS, WHERE ARE THE HUMAN PHENOTYPES? SO THERE ARE COGNITIVE BATTERIES THAT HAVE BEEN DEVELOPED THAT CAPTURE A RANGE OF COGNITIVE TRAITS THAT ARE RELATED TO CIRCUITS. SO IT IS FEASIBLE.

IF THERE IS GOING TO BE NEW RECRUITMENT OF PATIENTS, IT IS QUITE FEASIBLE TO DO COGNITIVE --

CHAIRMAN GOLDSTEIN: GREAT. THANK YOU VERY MUCH. SO WE'RE RIGHT UP, ACTUALLY WE'RE A COUPLE MINUTES LATE.

MR. TOCHER: LARRY, SORRY TO INTERRUPT. I DO HAVE JUST A -- THERE ARE A COUPLE COMMENTERS WHO SUBMITTED WRITTEN COMMENTS THAT I'VE BEEN ASKED TO READ.

DR. GASSON: I THINK 5193 WAS NEXT IN LINE. I DON'T KNOW WHERE IT WENT.

MS. DEQUINA-VILLABLANCA: I DON'T SEE ANY ADDITIONAL HANDS UP, RAISED. GO AHEAD, SCOTT.

UNIDENTIFIED SPEAKER: I THINK IT WAS NELSON FARMER WHO WAS HAVING DIFFICULTY UNMUTING FROM HIS PHONE.

MR. TOCHER: OKAY. WELL, LET ME PROCEED WITH THESE OTHERS WHILE WE WORK THAT OUT.

FROM DR. CARRIE BEARDEN OF UCLA, A

PROFESSOR OF THE DEPARTMENTS OF PSYCHIATRY AND BIOBEHAVIORAL SCIENCES AND PSYCHOLOGY, SAYS, "I WOULD LIKE TO STRONGLY ADVOCATE FOR CIRM FUNDING TO BE USED FOR RESEARCH ON MENTAL HEALTH AND NEURODEVELOPMENTAL DISORDERS. IN PARTICULAR, RARE NEUROGENETIC DISORDERS WITH LARGE EFFECTS ON NEUROPSYCHIATRIC PHENOTYPES HAVE STRONG POTENTIAL TO INFORM OUR UNDERSTANDING OF BROADER DISEASE MECHANISMS AND CAN BE READILY MODELED IN EXPERIMENTAL SYSTEMS SUCH AS MANIPULATION OF GENETIC BACKGROUND IN THE CONTEXT OF LARGE EFFECT MUTATIONS WHICH CAN PROVIDE VALUABLE INSIGHTS."

NEXT, "MY NAME IS NELSON FRAMER. I'M A PROFESSOR OF PSYCHIATRY AND HUMAN GENETICS AT UCLA FOR THE PAST TEN YEARS. I HAVE ALSO SERVED AS DIRECTOR OF UCLA'S DEPRESSION GRAND CHALLENGE. I WAS AN AUTHOR OF THE UCLA/UCSF WHITE PAPER THAT SEVERAL OF THE TASK FORCE MEMBERS HAVE ALREADY ALLUDED TO, AND THAT CALLED FOR CIRM TO MOUNT A MANHATTAN PROJECT FOR MENTAL HEALTH DISORDERS STARTING WITH STUDIES OF DIVERSE COHORTS TO IDENTIFY THE GENETIC VARIATIONS AND SOCIAL AND ENVIRONMENTAL FACTORS THAT CONTRIBUTE TO DISEASE RISK.

"I WISH TO EMPHASIZE THAT, WHILE OUR CAMPUSES ARE PARTICULARLY COMMITTED TO SUCH AN

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ENDEAVOR, WE ARE CERTAIN THAT INVESTIGATORS WITH RELEVANT EXPERTISE AT INSTITUTIONS THROUGHOUT THE STATE, BOTH WITHIN UC AND OUTSIDE OF IT, WILL BE EXCITED TO COLLABORATE. CENTRAL MOTIVATION PROVOKE MY OWN RESEARCH AND THE DEPRESSION GRAND CHALLENGE OVERALL IS THE BELIEF THAT THE GENERATION OF NEW KNOWLEDGE MUST FOCUS ON AND ENGAGE THE COMMUNITIES THAT HAVE HAD THE LEAST ACCESS TO MENTAL HEALTH CARE AND THAT DISPROPORTIONATELY BEAR THE BURDEN OF MENTAL HEALTH DISORDER, NOT JUST AS PARTICIPANTS IN NEW CIRM-FUNDED RESEARCH, BUT AS INTEGRAL PARTNERS IN PLANNING AND CARRYING OUT THIS WORK. ONLY BY DOING SO CAN WE DECREASE RATHER THAN INCREASE CURRENT INEQUITIES.

"THUS, WHILE I COMMEND CIRM FOR COMMITTING ITS CONSIDERABLE RESOURCES TO ADVANCING RESEARCH IN NEUROPSYCHIATRIC DISORDERS, I URGE YOU TO FOCUS ESPECIALLY ON STUDIES THAT WILL ADVANCE OUR KNOWLEDGE OF THE GENETIC VARIATIONS THAT SPECIFICALLY CONTRIBUTE TO DISEASE RISK IN THE DIVERSE POPULATIONS THAT HAVE BEEN IGNORED BY BIOMEDICAL SCIENCE, BUT THAT REPRESENT THE MAJORITY OF THE POPULATION OF OUR STATE.

"WE NOW HAVE THE TOOLS TO MAKE TRANSFORMATIVE ADVANCES, AND I'M CERTAIN WE'LL BE

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QUICKLY ABLE TO BRING TOGETHER THE INVESTIGATORS, CLINICIANS, AND COMMUNITIES THROUGHOUT THE STATE THAT WILL ENABLE US TO DO SO."

AND THEN BEAR WITH ME, ONE LAST COMMENT. I'LL GET THROUGH THIS AS QUICKLY AS I CAN. IT'S TWO PAGES LONG, BUT I'LL GET THROUGH AS MUCH AS I CAN IN THREE MINUTES.

"DEAR DR. GOLDSTEIN AND MEMBERS OF THE BOARD, THANK YOU FOR THIS OPPORTUNITY AND YOUR VISIONARY LEADERSHIP. THIS IS ON BEHALF OF BALJIC (PHONETIC) KECK, PROFESSOR OF PHYSIOLOGY AND NEUROSCIENCE AT THE DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA, AND NICOLA ALLEN, AN ASSOCIATE PROFESSOR OF NEUROSCIENCE AT THE SALK.

"TODAY WE ARE ADVOCATING ON BEHALF OF THE $1.5 BILLION CIRM BUDGET BE ASSIGNED TO THE STUDY OF -- THAT ONE-HALF OF THAT BUDGET BE ASSIGNED TO THE STUDY OF NONNEURONAL CELLS OF THE BRAIN. THE RANGE OF HUMANS AND OTHER VERTEBRATES COMPRISE TWO MAJOR CELL POPULATIONS, NEURONS AND NONNEURONAL CELLS THAT CO-EVOLVED OVER 600 MILLION YEARS. THESE CELLS WERE DISCOVERED AROUND 140 YEARS AGO. HOWEVER, FOR THE LAST 60 YEARS, MOST OF THE EFFORT HAS BEEN DEVOTED TO THE STUDY OF NEURONS BECAUSE OF THEIR IMPORTANCE AND PERHAPS BECAUSE THEY WERE THE

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MOST TECHNICALLY FEASIBLE AND SIMPLEST TO STUDY.

"THE NONNEURONAL CELLS THAT REPRESENT 50 PERCENT OF THE CELLS OF THE BRAIN HAVE BEEN LARGELY UNDERSTUDIED. THUS, AT A BASIC LEVEL, OUR UNDERSTANDING OF BRAIN DISEASES IS LIMITED BECAUSE WE SIMPLY DON'T KNOW ENOUGH ABOUT HALF OF THE BRAIN. IN THE CANCER REALM, IT'S LIKE TRYING TO TREAT TUMORS WHILE IGNORING THE VARIOUS TISSUE ENVIRONMENTS IN WHICH THEY RESIDE AND UPON WHICH THEY DEPEND. WE ALL KNOW THIS WOULD NEVER WORK.

"IN THE SAME WAY, IF WE ARE SERIOUS ABOUT UNDERSTANDING AND TREATING BRAIN DISEASES, THEN WE MUST BE SERIOUS ABOUT UNDERSTANDING HALF OF THE CELLS THAT HAVE BEEN IGNORED AND WE MUST INVEST IN THIS AREA NOW.

"THE LAST FEW YEARS HAVE SHOWN NONNEURONAL CELLS CONTRIBUTE TO TRAUMATIC BRAIN INJURY, VIRAL INFECTION, TUMORS, NEURODEGENERATION, AND PSYCHIATRIC DISEASES. THE EVIDENCE TO SUPPORT THIS VIEW COMES FROM NEUROPATHOLOGICAL STUDIES, POSTMORTEM TISSUE ANALYSIS, STEM CELL REPLACEMENT STRATEGIES, AND FROM GENETIC ANALYSES OF KNOWN AND CAUSATIVE GENES FOR HUMAN DISEASES.

"THE EVIDENCE THAT NONNEURONAL CELLS CONTRIBUTE TO ALMOST ALL BRAIN DISEASES AND THAT

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THEY ARE ESSENTIAL FOR SUCCESSFUL STEM CELL THERAPIES IS SIMPLY OVERWHELMING. A NEW OPPORTUNITY THEREFORE EMERGES TO IDENTIFY AND DEVELOP NEW THERAPEUTIC STRATEGIES. SCIENTISTS IN CALIFORNIA ARE POISED TO TAKE ADVANTAGE OF THIS NEW OPPORTUNITY, HAVING MADE MANY OF THE INITIAL BREAKTHROUGHS.

"HOW SHOULD WE MOVE FORWARD? SINCE HALF OF THE CELLS IN THE HUMAN BRAIN ARE NONNEURONAL, WE SUGGEST THAT HALF OF THE FUNDS BE DEDICATED TO THEIR STUDY IN HEALTH AND DISEASE. THIS COULD BE ACHIEVED THROUGH CURATED RFA'S TO STUDY NONNEURONAL CELLS IN NEUROLOGICAL OR PSYCHIATRIC DISEASES. ALTERNATIVELY, AND MORE EFFICIENTLY, IT COULD BE ACHIEVED BY THE FORMATION OF A HIGHLY CONNECTED CENTER WITHOUT WALLS OF RESEARCHERS DEDICATED TO THIS EFFORT AND DRAWING FROM ALL OF CALIFORNIA AND WORKING AT MULTIPLE LOCATIONS IN UNIVERSITIES, HOSPITALS, THE COMMUNITY, AND THE PRIVATE SECTOR. IF THIS VISION COULD BE ACHIEVED, IT WOULD BE A WORLD FIRST FOR HOW MODERN AND IMPACTFUL COLLABORATIVE WORK SHOULD BE DONE.

"WE URGE YOU TO EARMARK HALF OF THE CIRM FUNDS TO STUDY THE HALF OF THE BRAIN THAT HAS BEEN IGNORED --

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MS. DEQUINA-VILLABLANCA: TIME. THREE MINUTES IS UP, SCOTT.

MR. TOCHER: AND THAT'S IT.

CHAIRMAN THOMAS: OKAY. GREAT. I'M GOING TO TRY TO ADJOURN US AGAIN. LET ME THANK ESPECIALLY DR. JONATHAN SEBAT AND DR. BENJAMIN NEALE. YOU GUYS HAVE GIVEN US A LOT TO THINK ABOUT AND WHAT SEEMS LIKE PLENTY OF TRACTION TO MOVE INTO THE MODELING OF THESE DISORDERS. SO THANK YOU VERY MUCH FOR YOUR TIME. THANK YOU TO ALL THE COMMENTERS AND THANK YOU TO TASK FORCE MEMBERS WHO HAVE BEARED WITH US FOR TEN MINUTES PAST TIME.

SO LET ME ADJOURN US. THANK YOU ALL.

(THE MEETING WAS THEN CONCLUDED AT 12:09 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 TASK FORCE ON NEUROSCIENCE OF THE INDEPENDENT CITIZEN'S OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE IN THE MATTER OF ITS REGULAR MEETING HELD ON MARCH 13, 2023, 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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