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Instructions and Notes:

- Depending on the nature of what you are doing, some sections may not be applicable to your research. If so mark as “NA”.
- When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.

1 Protocol Title
Assessment of Customized Probiotic Therapy for Children and Adults with Autism Spectrum Disorder

2 Background and Objectives
Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

- Describe the purpose, specific aims, or objectives.
- State the hypotheses to be tested.
- Describe the relevant prior experience and gaps in current knowledge.
- Describe any relevant preliminary data.

Background:

Approximately 30-50% of children and adults with autism spectrum disorders (ASD) have chronic gastrointestinal problems, including constipation and/or diarrhea. Over-the-counter (OTC) probiotics are one of the most commonly used therapies by people with ASD, but there is only limited research on their efficacy, and those studies have used a “one-size-fits-all” approach for probiotic formulation. A new company, Sun Genomics, is now offering a customized probiotic based on testing of the person’s fecal microbiome (measuring the relative abundance of over 2300 different species), and then formulating a blend of OTC probiotic species for that individual. A typical blend contains approximately 6 different probiotic strains, all of which are classified as Generally Recognized As Safe (GRAS) by the FDA. The specific probiotic formulation for an individual is based on measurements of their individual microbiome. After 6 weeks, clients are invited to submit a new stool sample, and another round of microbiome testing is done, and a new probiotic is available after 12 weeks of treatment. This process can be continued for as long as the client wishes.

We propose to invite Sun Genomics customers who have ASD to participate in our research study, which is designed only to assess the outcome of Sun Genomics standard approach. The ASU research study involves: asking participants to fill out questionnaires (medical history, autism symptoms, and gastrointestinal symptoms), participate in a 30 minute phone interview to confirm autism diagnosis,, and to provide some additional stool (for microbiome and metabolite measurements) when they normally collect a stool sample for testing. Participants will consent for their stool sample to be further analyzed for research purposes by Sun Genomics and/or ASU.

Hypothesis: The customized probiotics developed by Sun Genomics will result in some changes in microbiota composition and some improvements in gastrointestinal (GI) and/or ASD symptoms.

Preliminary Data: Sun Genomics has already provided customized probiotics for thousands of clients, including 14 individuals with ASD. Their customer questionnaires reveal that many clients experience some improvement in GI symptoms. In particular, their ASD clients have reported improvements in both GI and ASD symptoms, including sleep, irritability, and more regular bowel movements.

3 Data Use
Describe how the data will be used. Examples include:

- Dissertation, Thesis, Undergraduate honors project
- Publication/journal article, conferences/presentations
- Results released to agency or organization
- Results released to participants/parents
- Results released to employer or school
- Other (describe)

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Sun Genomics provides its clients with a detailed summary of the measurements of their microbiome. The data that ASU collects will be shared with Sun Genomics, and survey data for participants collected at Sun Genomics will be shared with ASU, together with their measurements of the microbiome. Thus, we will have data before and after their customized probiotic treatment, and that combined data will be used for research publications, and intellectual property creation. For any intellectual property created the ownership will follow inventorship and Sun Genomics will have first rights to negotiate for exclusivity and non-exclusive should we not choose to exercise.

4 Inclusion and Exclusion Criteria

Describe the inclusion and the exclusion criteria for the study.

Describe how individuals will be screened for eligibility.

Indicate specifically whether you will target or exclude each of the following special populations:

- Minors (individuals who are under the age of 18)
- Adults who are unable to consent
- Pregnant women
- Prisoners
- Native Americans
- Undocumented individuals

Inclusion Criteria:

- 1) New client of Sun Genomics (has applied for testing and treatment, but not yet begun treatment)
- 2) Diagnosis of ASD (initially based on self-report of ASD diagnosis by appropriate medical professional, and then verified by an evaluation of the Social Responsiveness Scale (SRS-2) by ASU staff.
- 3) Children and adults ages 2.5-75 years

Exclusion Criteria:

- 1) Antibiotic use in the last two months (not counting topical antibiotics)
- 2) Any changes in medications, nutritional supplements, therapies, in the last two months, or any plans to change them during the first 3 months of probiotic treatment.

Screening For Eligibility: New clients of Sun Genomics will be asked if they have ASD, and if so they be directed to the landing page for enrollment.

Special Populations: This study is specifically focused on children and adults with ASD, because that group commonly uses OTC probiotics and we want to learn more, and carefully document the potential for OTC probiotics to change their microbiome and improve their symptoms.

5 Number of Participants

Indicate the total number of participants to be recruited and enrolled

- Provide a rationale for the proposed enrollment number
- What percentage of screened individuals will likely qualify for the study?

We plan to initially enroll up to 1000 participants.

The rationale is that:

- 1) At baseline (pre-treatment), this large size will allow us to conduct one of the largest assessments of microbiome in children and adults with ASD, coupled with a detailed assessment of their GI and ASD symptoms. This will allow us to investigate many factors, such as connections between the microbiome and GI and ASD symptoms, the connection between GI and ASD symptoms, age effects, gender effects, diet effects, and more. Note that we will also be able to compare the ASD group against the aged-matched healthy controls used by Sun Genomics to establish the reference range for their microbiome measurements.
- 2) After treatment, we will be able to compare microbiome, GI symptoms, and ASD symptoms against baseline evaluations. This will allow us to evaluate the possible effect of Sun Genomics' customized probiotics in an open-label fashion. The large sample size will allow us to conduct extensive evaluations to assess the possible effect of probiotic treatment on ASD and GI symptoms and on the microbiome. Analysis of this large database may also lead to improvements in the algorithm that Sun Genomics uses to customize probiotics for each individual client.

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6 Recruitment Methods

- Describe when, where, and how potential participants will be identified and recruited.
- Describe materials that will be used to recruit participants. (Attach copies of these documents with the application.)
- Does any member have a dual role with the study population?
-

We will advertise the study in six ways.

- 1) Sun Genomics will add a question to its online questionnaire for new clients when they initially sign up with Sun Genomics. The questionnaire will ask if they have ASD, and if so it will lead them to the official study ad (Sun Genomics version) for current customers.
- 2) Our research group (the ASU Autism/Asperger's Research Program) will send the official study ad (ASU version) to our email list.
- 3) Facebook, Google adwords, and LinkedIn ads will be create to make specific audiences aware of the study to determine if it is right for them
- 4) Posting the official study ad on the PI and co-PI's websites.
- 5) Media announcements to bring awareness to the launch of the study and resources to go find out more
- 6) Posting the flyer from Sun Genomics on their website and sending it by email
- 7) Posting the 3-minute video about the study on the ASU and Sun Genomics websites, and including it in emails.

The study ads will lead to an online application form, followed by an online consent form. (See attached). There will also be a phone number and email so that potential participants can ask any questions.

7 Study Timelines

Describe:

- The duration of an individual participant's participation in the study.
- The duration anticipated to enroll all study participants.
- The estimated date for the investigators to complete this study (up to and including primary analyses).

Each participant will spend approximately 4.5 months initially in the study (sample collection, 1.5 months to test the samples and create the individualized probiotic, and 3 months of probiotic therapy). They will have the option of continuing participation in the study for additional 3-month cycles as a subscription until they decide to cancel.

We expect that enrollment will require several years.

We expect that it will take several years to complete the study (enrollment, participation, analysis of data), but we will conduct preliminary analyses as the study progresses, and are likely to publish preliminary results on an initial group.

8 Procedures Involved

Describe and explain the study design. Provide a description of all research procedures being performed and when they are performed.

Describe procedures including:

- The documents/ measures / devices/ records /sampling that will be used to collect data about participants. (Attach all surveys, scripts, and data collection forms.)
- What data will be collected including long-term follow-up?
- All drugs and medical devices used in the research and the purpose of their use, and their regulatory approval status.
- Describe the available compensation (monetary or credit that will be provided to research participants).
- Describe any costs that participants may be responsible for because of participation in the research.

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This study only involves the collection of questionnaires, an interview with our CARS evaluator to confirm diagnosis of autism, and collection of additional stool at each time Sun Genomics normally collects stool samples.

Measures/Data:

Baseline:

One extra collection vial and one extra collection wand will be added to the standard stool collection kit sent by Sun Genomics to its clients, for measurement of microbiome and metabolics of stool.

Study participants will also complete the following questionnaires

Health, Diet, and Medical History (5 minutes)

Parent Global Impressions of Autism – baseline version (5 minutes)

Gastrointestinal Symptom Severity Scale (5 minutes)

Social Responsiveness Scale (SRS II) (10-15 minutes)

Study participants will be given the option to complete the following questionnaires for additional compensation:

Daily Stool Record (DSR): 1 minute/day for 14 days

Screen for Child Anxiety Related Disorders (SCARED) (10 minutes)

30 minute interview with ASU staff for a CARS-2 evaluation to confirm diagnosis of ASD and compare against SRS (for a limited number of participants depending on funding and staff availability).

At 6 weeks: When SunGenomics sends another stool collection kit to its clients, and an extra vial for collection of additional stool will be included.

After 3 months of customized probiotic, participants will complete the following questionnaires:

Changes in health, diet, and medical history

Parent Global Impressions of Autism – changes version

In addition, if parents completed the DSR, SRS, or SCARED, then they will be invited to complete those as well.

If participants wish to continue the study longer, additional vials for stool samples will be collected, and the same questions would continue to be asked every 3 months.

Treatment: The ASU study does not involve administration of the probiotic, since the study is only open to clients of SunGenomics who have ordered a probiotic from them.

Compensation: Participants will receive a discount of \$25 off their next purchase from SunGenomics for participation in the Baseline evaluation, and additional discounts if they conduct the DSR (\$15), SCARED (\$10). They will receive similar discounts for their next purchase for each additional 3-month evaluation that they complete. To encourage completion of surveys, return of samples, and on-going subscription Sun Genomics will offer reward points for additional discounts through its Reward Program from time to time.

Costs: There is no cost to participate in the ASU study. Participants will have already purchased their probiotics from Sun Genomics but not yet started it (after the purchase it takes about 6 weeks for stool samples to be tested, and for the customized probiotic to be sent to the family).

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9 Risks to Participants

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the participants related the participants' participation in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks. Reference this information when appropriate.

- If applicable, indicate which procedures may have risks to an embryo or fetus should the participant be or become pregnant.
- If applicable, describe risks to others who are not subjects.

There is a small risk of loss of confidentiality to study participants. We will minimize that risk by assigning a code number to each applicant. There is a risk of contact with fecal matter during the stool collection. Gloves are provided to minimize the risk.

10 Potential Benefits to Participants

Realistically describe the potential benefits that individual subjects may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit. Do not include compensation or benefits to society or others.

This study is focused on assessing changes in GI and ASD-related symptoms. Those scores will be reported to participants by SunGenomics.

11 Setting

Describe the sites or locations where your research team will conduct the research.

- Identify where research procedures will be performed.
- For research conducted outside of the ASU describe:
 - Site-specific regulations or customs affecting the research.
 - Local scientific and ethical review structures in place.

This study will be conducted by mail for collecting stool samples in their homes, and online for completing forms..
The study coordination will be conducted from ERC 452 on the ASU Tempe campus.
Testing of stool samples will be conducted at both the laboratory of Prof. Krajmalnik-Brown in Biodesign, and at Sun Genomics.

12 Multi-Site Research

If this is a multi-site study where you are the lead investigator, describe the processes you will use to ensure communication among sites, such as:

- Each site has the most current version of the protocol, consent document, and HIPAA authorization.
- Required approvals have been obtained at each site (including approval by the site's IRB of record).
- Describe processes you will use to communicate with participating sites.
- Participating sites will safeguard data as required by local information security policies.
- Local site investigators conduct the study appropriately.

n/a – this is a single-site study

13 Resources Available

Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform your roles. When applicable describe knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.

Describe other resources available to conduct the research: For example, as appropriate:

- Describe your facilities.
- Describe the availability of medical or psychological resources that participants might need as a result of any anticipated consequences of the human research.
- Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

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Prof. Adams, Prof. Krajmalnik-Brown, and their staff are very experienced at working with children and adults with ASD, and have conducted previous studies of GI symptoms and gut microbiota in and adults with ASD.

Prof. Krajmalnik-Brown laboratory is BSL2 and is equipped to perform DNA extractions, necessary PCR reactions, and chemical analysis for some metabolites. She has led the microbiome analysis for several autism studies, as well as other studies. Her laboratory will also conduct analyses of stool samples, including microbiome and metabolite composition.

Prof. Adams, Prof. Krajmalnik-Brown, and the president of Sun Genomics, Sunny Jain, will work together to train ASU and Sun Genomics staff who work on this project. All staff working on this project will also undergo CITI training.

Sun Genomics is a commercial laboratory offering integrated testing of microbiota in stool, followed by delivery of customized probiotics. Their solutions help reduce the confusion at the retail shelf when selecting a probiotic and provides transparency back to the customer on their gut composition. Founded in 2016, Sun Genomics is based in San Diego, CA where it operates a GMP probiotic facility along with a molecular microbiology lab.

14 Prior Approvals

Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site, funding agency, laboratory, radiation safety, or biosafety approval.)

15 Data Management and Confidentiality

Describe the data analysis plan, including procedures for statistical analysis.

Describe the steps that will be taken to secure the data during storage, use, and transmission.

- Training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data

Describe how data and any specimens will be handled:

- What personal identifiers will be included in that data or associated with the specimens?
- Where and how data or specimens will be stored?
- How long the data or specimens will be stored?
- Who will have access to the data or specimens?
- Who is responsible for receipt or transmission of the data or specimens?
- How will data and specimens be transported?
- If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens.
- Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

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Documents with the patient identifiers will be stored separately from the samples and the sample coordinator will have access to the identifiers that link the codes. The researchers will not have access to this information – only number coded samples and questionnaires with matching numbers assigned to them will be available to the researchers doing this analysis.

Personal identifiers that will be included in that data or associated with the specimens: Gender and age, collection kit barcode, sample barcode

Specimens: Stool samples with barcodes will be stored in a -80 °C freezer at Sun Genomics in a secured space ,a portion of the collection will be transferred to the ASU Biodesign Institute alongside relevant de-identified data collected during sample analysis. Stool samples will be stored for up to 10 years.

Access to data or specimens: All PIs will have access to un-identified samples and un-identified data collected (i.e., code numbers only). The study coordinator will have access to all the data. Patient-specific data will be separately stored in a secure 256-AES encrypted folder in a hosted server with restricted access managed by SunGenomics. Sun Genomics and PI's will determine who has access to this information. Sun Genomics and its business associates follow HIPAA compliance standards. .

SunGenomics will send the results of their standard microbiome testing as de-identified data (by code number) to ASU.

Data release: De-identified data will be published in scientific journals

16 Safety Monitoring

This is required when research involves more than Minimal Risk to participants. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor. Describe:

- The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether participants remain safe.
- What data are reviewed, including safety data, untoward events, and efficacy data?
- How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).
- Who will review the data?

This study involves less than minimal risk so we do not plan on any safety data monitoring.

17 Consent Process

Describe the process and procedures process you will use to obtain consent. Include a description of:

- Who will be responsible for consenting participants?
- Where will the consent process take place?
- How will consent be obtained?
- If participants who do not speak English will be enrolled, describe the process to ensure that the oral and/or written information provided to those participants will be in that language. Indicate the language that will be used by those obtaining consent. Translated consent forms should be submitted after the English is approved.

Since this is a simple study, we will simply add an invitation to the Sun Genomics website to invite their customers with ASD to participate in this study, with a study ad and a link to the consent form if they are interested. An email address and phone number for ASU staff will be listed so that people can ask if there are any questions. The study will be limited to English speakers. For children age 7 and older there is an assent form for them to review and sign if they wish to participate.

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18 Investigational New Drug or Devices

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

- Identify the hold of the IND/IDE/Abbreviated IDE.
- Explain procedures followed to comply with FDA sponsor requirements for the following:

FDA Regulation	Applicable to:		
	IND Studies	IDE studies	Abbreviated IDE studies
21 CFR 11	X	X	
21 CFR 54	X	X	
21 CFR 210	X		
21 CFR 211	X		
21 CFR 312	X		
21 CFR 812		X	X
21 CFR 820		X	

N/A

19 CITI

Provide the date that the members of the research team have taken the CITI training for human participants. This training must be taken within the last 4 years. Additional information can be found at: <http://researchintegrity.asu.edu/training/humans>

James B. Adams May 12 2020
Rosa Krajmalnik-Brown – May 4 2017
Elena Pollard – May 4 2017
Carlos Robles – Oct 29 2019
Pompa Bhattacharjee – June 1 2020

Sun Genomics staff:
Sunny Jain – July 15, 2020
Neal Gidvani – June 23, 2020
Sherilyn De Leon – June 25, 2020
Kevin Taugher – July 2, 2020
Jesse Lake Youngberg – July 1, 2020
Eric Cutter – July 2, 2020
Megan Reynolds – July 29, 2020
Caroline Flynn – June 26, 2020
Zenas George – February 24, 2020
Divya Nair – July 9, 2020
Demi Flores – July 3, 2020
Andre Nguyen – July 1, 2020
Thibaut Montagne – July 17, 2020
Shirin Treadwell – July 20, 2020
Summer Dietsche – July 13, 2020