BD² Breakthrough Discoveries for thriving with Bipolar Disorder

# Genetics Program Request for Applications (RFA)

**September 2022**

## Executive Summary

We invite you to apply for the BD²: Breakthrough Discoveries for thriving with Bipolar Disorder Genetics Program. This program seeks to significantly contribute to the genetic database of individuals with bipolar disorder by performing genetic sequencing on a large, diverse population of people with bipolar disorder. We will fund one institution or one consortium of institutions that has access to a large number of diverse samples of DNA from people with bipolar disorder and a matched control population. The institution(s) must have the capability to perform whole genome or whole exome sequencing and must share the resulting de-identified data with the research community. BD² intends to commit up to $10 million in 2023 to support the genetics program for up to two years. We welcome applications that feature multiple organizations that are proposing a coordinated effort. BD² intends to fund one application and award up to $10 million over two years.

## Background

Bipolar disorder is a highly complex and heterogeneous disorder that is often debilitating. Even though it is prevalent in about 3% of individuals worldwide, little is known about its underlying biology. There is ample evidence of the strong role of genetics in bipolar disorder, but the exact genes and genetic variations involved in its etiology are not fully understood, and progress is hampered by the lack of sufficient samples and sequencing on samples from individuals with bipolar disorder. Advancements in our understanding and treatment of bipolar disorder to date remain far from ensuring that everyone living with bipolar disorder can manage their condition and lead independent, fulfilling lives.

BD² is a collective force to transform what we know about and how we treat bipolar disorder. It is a commitment to the 40 million people living with bipolar disorder, those not yet diagnosed, and their loved ones.

The Baszucki, Brin, and Dauten families united with the Milken Institute to create BD² to advance discoveries for families like theirs. For too long, there have been limited advances in the study and treatment of bipolar disorder due to lack of collaboration and funding. It's time for a new approach.

The BD$^2$ Genetics Program seeks to advance our understanding of bipolar disorder genetics, including nuclear and mitochondrial genetics. The program will provide funding to sequence a large number of samples of DNA from a diverse group of people diagnosed with bipolar disorder. Inclusion of individuals from non-European ancestries is a high priority. We intend to support an applicant who not only can perform this type of sequencing and analysis but also will adhere to our guiding principles of collaboration and open access to accelerate the development of effective interventions for bipolar disorder.

# The Opportunity

Throughout the decades of bipolar disorder research, it has become clear that research strategies must shift drastically to ensure faster and more significant discoveries. Philanthropic support has presented a once-in-a-generation opportunity to develop a unique mechanism to bring the most capable and innovative minds together to explore one of the most complex mental disorders.

The field has the opportunity to examine novel genomic variations associated with bipolar disorder by performing genetic sequencing on a large and diverse group of individuals with bipolar disorder. Funded organization(s) will collectively receive up to $10 million over two years to gather, sequence, and share the results of genetic data with the research community. Applicants will decide how the total $10 million will be split among organizations within their proposed consortium. The funded applicant will be directed by a dedicated Scientific Steering Committee (SSC) and the BD$^2$ program team to ensure that awardees are able to share resources, data, successes, and challenges throughout the funding period.

Ideally, applicant organizations should already have access to many samples of people with bipolar disorder, who are also of diverse backgrounds. Applicants should have deep expertise in genetics and genomics of bipolar disorder or other psychiatric disorders and have infrastructure at the ready to perform and analyze whole genome (including mitochondrial genome) or whole exome sequencing within the two-year award period. The selected organization(s) shall provide the data back to the research community, in an open access manner, to expedite scientific advancements.

## Commitment to Open Science

Open science is a key governing philosophy of BD$^2$, as it will allow for rapid and efficient sharing of new knowledge, catalyzing novel hypotheses to test. Funded investigators will be expected to adhere to BD$^2$'s open science policies, including pre-print submissions, and sharing protocols and datasets to pre-approved repositories. Teams and their affiliated institutions should review our Open Science Policy prior to submission.

## Important Dates

- September 12, 2022: RFA released
- November 11, 2022: Applications due
- November 2022 – February 2023: Application review and potential site visits
- April 2023: Award announced

# Eligibility Criteria

## Organizational Eligibility

Applications will only be considered from teams who meet all eligibility criteria below:

- Each applicant organization must be a non-profit academic or research organization, including domestic and non-U.S. non-profit organizations, domestic and non-U.S. public/private academic universities, or institutions of higher learning (including colleges, universities, medical schools, and other related academic research organizations). Certain governmental agencies with active biomedical research programs may also apply.
- The selected organization(s) must have access to an existing cache of genetic samples from a diverse group of people with bipolar disorder via the organization's own efforts or through partnerships with other organizations. The number and diversity of samples will inform the assessment process.
- The selected organization(s) must make the resulting de-identified genetic sequences readily available for the research field as soon as possible. Data accessibility will be an important part of the selection criteria.
- The existing cache of genetic samples to which the selected organizations will have access must be available for use in research based on consents from the individuals whose samples are within the cache or a waiver of or exception to the requirement for such consents.
- The selected organizations must provide the genetic samples in de-identified form, adhering to the standards for de-identification set forth in the Health Insurance Portability and Accountability Act (HIPAA) privacy regulations, 45 C.F.R. § 514(b).
- The selected organizations must have an understanding of and proven ability to comply with applicable data protection regulations, including the privacy and security regulations implementing HIPAA.
- If more than one organization is identified in the application, one organization shall be proposed as the lead applicant organization, and the others included as sub-grantees. A Lead Principal Investigator (PI) who is affiliated with the lead applicant organization submitting the application must be identified. Every other organization on the application must also identify a co-PI to lead efforts at their respective organizations.
- The selected organization(s) may not subgrant any funding awarded to those organizations outside of those named in the application without approval, in writing, from the scientific leadership and program staff of the BD$^2$ Genetics Program.

## Leadership Eligibility

- A Lead PI must be identified for each application. The Lead PI is responsible for the scientific and technical direction, oversight, and management of the program. The Lead PI's organization is responsible for contractual and financial obligations, and other organizational assurances and certifications. It is highly encouraged that the Lead PI have demonstrated experience in psychiatric genetics. The Lead PI will submit the application and be the primary point of contact between their team and the BD$^2$ staff during the submission and selection process, as well as throughout the award period for progress reporting and other matters.
- Lead PIs and co-PIs must hold a doctorate (e.g., Ph.D., M.D.) or related research doctorate degree.

### Ineligibility

- Organizations that have no expertise in psychiatric genetics, access to samples, or sufficient expertise and infrastructure to perform whole genome or exome sequencing within the allotted two-year timeframe and allotted budget should not apply.
- This grant will not fund the initiation of new sample acquisition or significant infrastructure buildout to perform the required assays. Applicants should have access to existing samples ready to be sequenced and/or analyzed and the majority of existing personnel and equipment.

## The Application

Applications should include a detailed scientific rationale and operational aspects of the proposed project. All applications will be submitted via the Submittable online grant portal. All Lead PIs must create an account to access the portal and submit applications. Required supplemental materials include letters of organizational commitment, a detailed budget, and the Lead PI's Biosketch. The application is due **November 11, 2022**.

### Application Details

A five (5) page application shall be submitted by the Lead PI. An application with multiple organizations must identify a Lead Organization. The Lead PI must be from the lead organization and submit the application. The application should discuss the organization's and leadership's psychiatric genetics expertise, the organization's infrastructure, access to samples, commitment to open science, and a milestone-based timeline. Each section does not have a specified length; the only length requirement is that the application shall not exceed five (5) pages. See below for required sections within the application.

**Overarching Strategy**
Describe the overarching strategy that your team intends to implement in this proposed research. This strategy should include:

- A description of the team's sequencing strategy, such as choosing whole exome versus whole genome approaches, and how this will meet the goals of improving our understanding of the biology of bipolar disorder. A related consideration is whether a chip-based GWAS should be performed in parallel to the sequencing. Additionally, the application should specify the team's capabilities to evaluate mitochondrial genetics from whole genome studies and/or mitochondrial DNA sequencing.
- An advanced data analysis strategy to be used once the sequences have been complete.
- The data sharing strategy that will be used to communicate data and findings to the field.
- If applicable, how you intend to communicate and collaborate with potential organizations in your grant.

**Psychiatric Genetics Expertise**
Describe the psychiatric genetics expertise of the Lead PI and the lead organization. Include specific papers, affiliations, partnerships, results, or any other evidence of the applicant's expertise. Discuss expertise in performing whole genome or exome sequencing on large quantities of biosamples, genetic data storage, analysis, and sharing with the broader research community. A major consideration is the rationale for the choice of whole genome or whole exome sequencing in your application.

**Infrastructure and Personnel**
Outline the organization's current infrastructure that would allow for whole genome or exome sequencing of large quantities of DNA samples. This includes infrastructure and personnel to:

- Accept and store large quantities of biosamples;
- Extract DNA from blood;
- Perform whole genome or exome sequencing;
- Perform other types of genetic sequencing, such as mitochondrial DNA sequencing; and
- Maintain and conduct data storage, data analysis, and data sharing.

This section should also:

- Outline the applicant's proven understanding of and ability to comply with the HIPAA privacy and security regulations and all other data protection requirements applicable to the research to be conducted; and
- Specifically outline the equipment and staff currently available at the organization(s) and the outstanding equipment to be purchased and additional personnel needed to be hired to operationalize the program. If the application has more than one organization, specify the organizational affiliation of the relevant equipment and personnel.

**Sample Description**
Provide a narrative description of samples that are available. Note that a template to disclose the full inventory and list of characteristics and demographics will be required in the application. This can be found in the grant portal. A full description includes:

- Sample type (i.e., blood, saliva, etc.).
- Sample amount and demographic features (racial, ethnic, gender, geographic, etc.).
- Note: Robust inclusion of individuals from non-European ancestries is a high priority.
- Sample diagnostic information, if available (BD I, BD II, schizophrenia, etc.).
- Any other accompanying phenotypic information that would be attached to the individual from whom the sample was acquired. This includes health records, actigraphy data, biosample readouts, or clinical data.
- Control sample size and demographic information.
- Any ability to follow up to collect additional biosamples from participants in the sample set.
- Level of access to the samples (i.e., whether your organization has sole access, or whether it must be shipped from a collaborator).

**Commitment to Open Science**
Describe your organization's current policies and actions that speak to encouraging an open scientific enterprise. This includes sharing data with other organizations and with the research community, participation in current psychiatric genetic efforts such as the Psychiatric Genetics Consortium, and any open science publication practices such as membership in cOAlition S. This also includes comingling or connecting these datasets with datasets from sequencing efforts in relevant disease areas such as depression, schizophrenia, autism, and neurodegeneration.

**Projected Timelines and Milestones**
Provide a detailed milestone-based timeline for the two-year award period, starting with receipt of funds, estimated for June 2023. Milestones include:

- Access to biosamples;
- Initiation of sequencing;
- Point of optimal performance;
- Initiation and completion of data analysis; and
- Release of sequencing data to outside researchers.

## Letters of Commitment

- **Organizational commitment:** Each application must include a letter of commitment that demonstrates the organization's commitment to administering the grant according to a written grant agreement to be entered into between the selected organization and BD$^2$. The letter shall be signed by a department chair or a relevant authorized organizational representative, such as the Dean of Sponsored Research. Applications with multiple organizations must include a signature from a relevant authorized organizational representative from each organization.
- **Principal Investigator commitment:** An additional letter must state that each PI represented in the application is willing and able to commit to leading this project, to communicate regularly with program staff and the Scientific Steering Committee as needed, and to adhere to open science principles. The letter shall be signed by the Lead PI and all co-PIs.

## Detailed Budget

A detailed budget in USD, using the provided template: Acceptable expenditures shall include salary, fringe benefits, equipment, software, storage, reagents, project-related travel, and up to 15% indirect costs to support organizational infrastructure. Note that publication costs to open access journals will be covered by BD$^2$ and do not need to be budgeted in your proposal. The Lead PI's organization shall be proposed as the applicant organization and any other organizations shall be included as sub-grantees, managed by the applicant organization. Each collaborating site must outline their subaward budget to clarify needs for all parties. The budget must not exceed $10 million over two years.

- The maximum allowable budget is inclusive of 15% indirect expenses. For applications including a sub-grantee, the maximum allowable indirect rate across both grantee and sub-grantee organizations remains 15% of the total award budget.
- For international applicants: Please note grants will be made in USD, and BD$^2$ is not responsible for changes in conversion rates.
- Grants selected for funding will be made payable to the applicant's organization. Under no circumstances will funding be paid to an individual. Please note that funds will be disbursed on an annual basis to the Lead PI's organization.

## PI Biosketch

A biosketch of the Lead PI and co-PIs, utilizing the NIH template, is required and shall not exceed five (5) pages per PI. If the Lead PI or co-PI does not have a biosketch in an NIH template, a CV is sufficient.

# Review Process

The written applications will be reviewed by the scientific leadership and program managers of the BD² Genetics Program.

## Application Review

Our review criteria will be based on the characteristics outlined below:

- **Psychiatric genetics expertise:** The lead PI, relevant staff associated with the application, and the organization(s) have robust psychiatric genetic expertise. Expertise in bipolar disorder genetics is preferred.
- **Infrastructure:** There is ample existing infrastructure necessary to perform the required tasks and activities necessary to sequence large numbers of samples. There is little required in hiring new staff or purchasing additional equipment to handle the volume.
- **Access to samples:** The organization, or consortium of organizations, has direct access to a large number of samples from people with bipolar disorder. No minimum number is required, but the samples should provide sufficient statistical power to advance our understanding of bipolar genetics. The samples should be from a diverse group of individuals including diversity as to gender and ancestral origin. Collection of samples that focus on groups traditionally under-examined in bipolar disorder genetics will also be considered.
- **Commitment to open science:** Open science and substantial collaboration by the applicant organization has been evidenced in previous and current partnerships, publications, and actions. The commitment to open science as described in the application is thoughtfully written and operationally feasible.
- **Projected milestones:** The milestone-based timeline highlights the ability to complete the sequencing task within two years. Milestones are realistic, affordable, and clear.
- **Cost realism:** A realistic budget adequately supports personnel, equipment, overhead, and other needs to carry out the project.

## Potential Site Visits and Virtual Interview

As needed, finalists may be asked to host a site visit or be interviewed virtually by members of the review committee. Details for site visit or virtual interview requirements will be provided to finalists.

## Final Selection

Following the site visit, the SSC of BD² will convene to provide recommendations of the final applicant to support the BD² Genetics Program. Final decisions will be confirmed by the Program Board. Once notified, the awardee will work with the program team to implement the program.

# Grant Terms and Policies

Each funded organization will be required to co-sign and agree in writing to BD²'s grant terms within thirty (30) days from receipt of notice of the award and prior to funds being released. BD²'s grant terms include, but are not limited to, the following items.

## Use of Funds

Each team will be applying for a grant that would provide up to $10 million over two years. Because applications may be partially funded, teams will receive the amount that is sufficient to carry out the aims that are selected for funding.

- **Use of funds:** Funds may be used for scientific and technical personnel, supplies, and standard equipment needs directly related to the successful execution of the proposed scope or work. This also includes travel to relevant conferences and events. However, funds may not be used for laboratory or facility renovation.
- **Carryover funding:** Unused research funds may be carried over to the following year, with approval, and requests for no-cost extensions will be considered.
- **Indirect costs:** Indirect costs are included in the $10 million award over two years. Up to 15% of the entire grant budget may be slated for indirect costs. Note that awards may be lower than the maximum $10 million per year. In such a case, only up to 15% of that specified grant budget may be allocated to indirect costs.
- **Unexpended funds:** Any funds not expended or committed for the purposes of the grant by the conclusion of the grant term must be returned to BD² unless otherwise agreed to by BD² in writing.
- **No cost extensions:** No cost extensions can be requested by teams within the last year of the award period.
- **Supplemental funding:** If a funded organization proposes to supplement any funds provided by BD² with funds provided by a third party, the organization must first provide notice to BD² and must ensure that the funding terms associated with any such third-party funds do not preclude sharing of data or publication or project results as outlined in this RFA.

## Data Sharing Protocols

Open and responsible data sharing is a key tenet to avoiding roadblocks and delays in research findings. Therefore, data sharing and open science are key pillars of the BD² Genetics Program. Teams and their affiliated institutions should review and confirm that they can comply with our Open Science Policy prior to submission.

- **Open access:** All data resulting from the genetic sequencing of this effort will be available to the scientific community at large at the earliest opportunity on preprint servers, online protocol platforms, and in an open access journal format.
    - **Publications:** All publications related to this funded work must be submitted to a preprint server, such as bioRxiv, before or concurrent with the first submission to a journal. An open access journal format is a requirement of this funding opportunity. Experimental protocols should be made publicly available through a protocol sharing service, such as bio-protocol or protocols.io. Scientific publications, preprints, and presentations that result from BD² awards are required to acknowledge support from BD².

- **Data and code sharing:** All datasets and code, either curated or generated through the project, must be made publicly available and easily accessible online, as early as possible when feasible. This includes metadata, documentation, and intended computational use cases, as appropriate. BD² scientific leadership will work with the funded applicant to identify appropriate data platforms.

- **Reporting requirements:** Progress reports with financial report-outs are due annually or at other times as deemed necessary by the scientific leadership for project evaluation. Progress report forms will be provided by the BD² Genetics Program administrative staff.
  - Quarterly progress discussions will be held between program administrators and the PIs of each team. Where necessary or helpful, follow-up could be expected.

### Intellectual Property

Intellectual property resulting from, created, developed, conceived, or reduced to practice in whole or in part with funding from BD², including all patent, copyright, trademark, trade secret, and other rights therein (Grant IP) would be subject to obligations on the recipient organization to:

- Commercialize any Grant IP that has the potential to benefit patients who have bipolar disorder;
- Allow BD² or its sublicensee to commercialize any such Grant IP that the grantee is unwilling or unable to commercialize;
- Widely disseminate through publication the results of research funded with grants from BD²; and
- Grant a research license to BD², the founding funders of BD², and all of their respective non-profit grantees to use and to practice Grant IP in the field of bipolar disorder.

## Funding Awarded in BD²'s Discretion

Responding to this RFA and/or submitting an application does not entitle any individual or organization to receive funding from BD². Funding, if any, would be provided in BD²'s sole discretion pursuant to the terms of a written grant agreement executed by BD² and the selected grantee organization, the terms of which BD² may require to be acknowledged by the PI.

## Contact Information

An automated email confirmation is generated upon application submission. If you do not receive confirmation within 24 hours of submitting your application, please check spam filters, then contact DiscoveryGrants@BipolarDiscoveries.org.

For inquiries about scientific priorities, eligibility requirements, application submission, as well as general and media inquiries, please contact: DiscoveryGrants@BipolarDiscoveries.org.