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Title: Analysis of Trends in Funding of Metastatic Breast Cancer Research

Introduction: To inform funding strategies for research in metastatic breast cancer (MBC), knowledge of the current research landscape and identification of potential gap areas requiring additional research are essential. In 2014, the Metastatic Breast Cancer Alliance (MBCA) published an analysis that showed that between 2000 and 2013, only 7% of all funds for breast cancer research were devoted to metastasis. As more people are living with MBC, addressing research priorities for those living with the disease is important, as is understanding gaps in the current funding landscape of MBC research to appropriately target investment. **Methods:** A collaborative effort between funders and patients was undertaken to analyze breast cancer projects funded between 2014 and 2020 from the International Cancer Research Partnership database, the Health Resource Alliance database, and MBCA members, representing grants from 83 non-profit organizations worldwide. Project titles, abstracts, and classifications of these grants were extracted from these databases. Next, to identify research projects in the databases that are related to metastasis, a classification tool that uses a machine learning algorithm was built, trained on manually coded grants from the 2000-2013 analysis, and validated by expert coders. Projects were then coded according to a pre-established metastasis classification policy to categories such as type of research (e.g., treatment), genes or proteins studied, site of metastasis, breast cancer subtype, and patient priority questions. In terms of the latter, MBCA members living with MBC were surveyed about research priorities. Member advocates ranked survey questions according to highest patient priority, and these were converted to language that could be queried with the tool. Results: Investment in MBC research nearly doubled from 2014 to 2020. Research into understanding and overcoming treatment resistance, which was the highest patient priority question, increased from 15% in 2014 to 26% of the MBC portfolio in 2020; this was a statistically significant increase above the rate of inflation. In terms of treatment resistance according to subtype, the highest number of projects focused on triple-negative

MBC (>300). By contrast, <20 projects were focused on overcoming treatment resistance in metastatic invasive lobular breast cancer. Of the six categories evaluated (e.g. biology and detection/diagnosis/prognosis), the largest increase in investment was for treatments. **Discussion:** The coding tool allows for ongoing complex queries such as identification of funded research relevant to areas identified as important by MBC advocates (Table) and provides a funders' 'dashboard' to identify gap areas in need of further research funding. This collaborative effort between funders and patient advocates, and the resulting current and future analyses, can be used to focus advocacy efforts to drive research funding of priorities and understudied areas of MBC. Despite the increase in funding, the investment in metastatic research—the primary cause of death from breast cancer—remains insufficient.

Table: Research Priorities of MBC Patient Advocates

	rch Priorities of MBC Patient A Biology, Translational, and	New Drugs and	Quality of Life	Technology
	Clinical	Treatments	,	07
Top Priorities	-Identify and define the role of somatic genes in metastatic tumors and the role of tumor heterogeneity in the selection of treatments for MBC	-Understand how treatment resistance can be overcome in different subtypes -Define subsets of triple-negative MBC and appropriate treatments for those subsets -Identify better treatments for brain metastases and central nervous system metastases	-Research that identifies how side effects of treatments can be better managed	
Secondary Priorities	-Understand the immune system in each subtype and its potential role to keep metastasis in check and/or treat metastasis -Explore analysis of the tumor microenvironment to explain disease progression or help identify treatments -Identify the role of BRCA1, BRCA2, and other inherited genes in the development, progression, and treatment of MBC -Explore if the collection of serial biopsies in patients reveals the progression of MBC in various subtypes and identify if they are being tested in the clinic -Identify research that explores how bone metastasis impacts the spread of disease to other sites -Understand if pregnancy is a risk in developing MBC. Identify how many grants are looking at pregnancy and MBC	-Identify effective treatments for HER2-positive low tumors -Conduct comparative research between the three CDK4/6 inhibitors to determine which can all be used by the same patient -Identify effective treatments for lobular MBC -Identify better treatments for inflammatory breast cancer -Compare biosimilars to Herceptin to determine if they are as effective as Herceptin -Identify new treatments that strengthen bones, lessen osteoarthritis, and reduce pain in patients with bone metastases		-Develop imaging that will identify the presence of lobular breast cancer and/or the progression of lobular breast cancer in patients -Conduct research that helps to establish new clinical guidelines for imaging newly diagnosed MBC patients for brain metastases -Research and define the abscopal effect in which radiation of one area results in shrinkage of tumors in other places -Research and define the use of Stereotactic Body Radiation Therapy as a treatment for oligo metastasis or oligo progression and its effect on overall survival