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TITLE: Tumor Genomic Profiling in Breast Cancer Patients Using Targeted Massively Parallel Sequencing

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14. ABSTRACT The overarching goal of this proposal is to use massively parallel sequencing to detect somatic genomic alterations in breast cancer tumor samples in order to identify genetic determinants of tumor behavior that may inform clinical decision-making. We have developed a targeted sequencing platform that interrogates ~450 genes that are known to be altered in breast cancer and other cancers. We now plan to utilize this platform to study 150 tumor samples from women with ER+ breast cancer who have had early-, late- or no relapse following endocrine therapy. We have also sequenced tumor samples from patients with advanced breast cancer. To date, we have obtained metastatic tumor biopsies from 72 patients with ER+ breast cancer and successfully performed whole exome sequencing on 32 patients. Sequencing is being completed on the remaining 40 patients. Analysis of all patients will be conducted once sequencing is complete. In addition, we have performed whole exome sequencing on metastatic tumor biopsies from 65 patients with HER2+ breast cancer. For the subset of these 137 patients who have resistance to targeted therapies, analysis of pre-treatment tumor tissues is currently underway.					
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1. INTRODUCTION:

Knowledge of genetic changes that occur in cancer cells should ultimately facilitate individualized approaches to cancer treatment. However, methods to systematically profile cancers for relevant genetic changes in the clinical setting remain underdeveloped. The overarching goal of this proposal is to use cutting-edge genomic technology (massively parallel sequencing) in patients with breast cancer to identify genetic determinants of tumor behavior that may inform clinical decision-making. Two unmet clinical challenges in breast cancer motivate this approach. The first is the need for improved biological understanding of early stage estrogen-receptor positive (ER+) tumors with a high risk of recurrence. Systematic genetic profiling of early stage ER+ tumors may identify specific subsets of breast cancer and predict which patients are most likely to relapse. Second, there is a clear need for novel therapeutic strategies in metastatic breast cancers that have become resistant to standard therapies. Systematic genetic characterization of these resistant cancers might teach us about new therapeutic strategies or guide the development of targeted drug combinations that may help to overcome cancer drug resistance. This study aims to profile a clinically annotated cohort of 150 ER+ breast tumors to look for genetic differences in both early-recurring and late-recurring tumors. In addition, we aim to prospectively profile 50 patients with advanced breast cancer in order to study the impact of our approach in a setting that may ultimately inform clinical decision-making.

2. KEYWORDS:

Breast Cancer
Estrogen Receptor
Resistance
Recurrence
Massively Parallel Sequencing
Next Generation Sequencing
Targeted Sequencing
Whole Exome Sequencing
Genomics
Personalized Medicine
Precision Medicine

3. OVERALL PROJECT SUMMARY:

AIM #1: To perform genomic profiling across a clinically annotated cohort of ER+ breast tumors

The goal of this Aim is to establish a breast-cancer focused mutation profiling platform and use it to study an annotated collection of tumor samples from patients with ER+ breast cancers. During the course of this award, we successfully designed and constructed a targeted sequencing platform that can be used on FFPE tumor samples. This platform targets all known breast cancer related genes identified in large sequencing studies of breast cancer samples from the past several years, including several novel genomic alterations that we and others have recently identified in ER+ breast cancer samples. This platform is now being deployed on a cohort of tumor samples from patients with ER+ breast cancer who have had early recurrence, late

recurrence, or no recurrence at 10 years.

AIM 1A: To develop a breast cancer-focused massively parallel sequencing platform for FFPE samples

4 large sequencing studies (published in *Nature* in 2012) used whole exome and/or whole genome sequencing to catalogue the landscape of genomic alterations in primary, treatment-naïve breast cancers¹⁻⁴. In total, 819 primary breast cancers were sequenced across these 4 studies, of which 529 were

Study	Total Number of Breast Tumors	Total Number of ER+ Tumors
Stephens et al ¹	100 primary tumors	79 ER+ primary tumors
Banerji et al ²	108 primary tumors	60 ER+ primary tumors
Shah et al ³	104 primary tumors (triple negative)	0 ER+ primary tumors
TCGA ⁴	507 primary tumors	390 ER+ primary tumors
TOTAL	819 primary tumors	529 ER+ primary tumors

Table 1: Large-scale sequencing studies in breast cancer

ER+ (Table 1). A fifth study by Matthew Ellis and colleague⁵ reported the sequencing of 77 pretreatment tumor biopsies (46 whole genomes and 31 whole exomes) from patients with luminal breast cancer treated with a neoadjuvant aromatase inhibitor. This study was designed to identify genomic biomarkers that may predict response or intrinsic (*de novo*) resistance to endocrine therapy. Based on Ki67 levels in the surgical specimens, samples were stratified into AI-sensitive (Ki67 < 10%, n = 48) and AI-resistant samples (Ki67 > 10%, n = 29). Mutations in *MAP3K1* and possibly *GATA3* were associated with AI-sensitivity, while *TP53* mutations were associated with the AI-resistance. In the aggregate, these five studies have shed tremendous light onto the genomics of primary treatment-naïve breast tumors.

As described in our original research proposal, we developed an enriched set of genes including these new significantly altered genes identified in breast cancer, as well as numerous other novel cancer genes that have recently been identified. **In total, this design included all of the exons from 435 genes, selected introns to identify translocations from 22 genes, more extensive tiling across the entirety of 23 genes, and the promoter of the TERT gene.** The resultant list of genomic coordinates were optimized and a set of baits were designed and synthesized. We completed testing and implementing of this platform, as described in our original research proposal.

More recently, we identified several novel alterations in ER+ breast tumors, including translocations in *ESR1*, the gene that encodes the estrogen receptor (Wagle, Garraway, and Arteaga, unpublished results). Given the potential importance of ESR translocations in ER+ breast cancer, we then further modified our bait design to include genomic coordinates across select introns in *ESR1*. In addition, two recent papers from the Broad Institute published in *Nature* in 2013 highlighted several novel cancer genes not previously identified as significant in cancer^{6,7}. All of these alterations were also added to our targeted sequencing panel design, and a 2nd iteration (v2.0) was then developed. This v2.0 targeted sequencing panel is particularly well suited to profiling ER+ breast tumors.

TASKS:

- Design and optimization of breast-cancer specific platform (Month 1 – Month 4): **COMPLETE**

AIM 1B: To perform genomic profiling across a clinically annotated cohort of ER+ breast tumors

In this aim, we proposed to use our breast-cancer focused platform to profile a cohort of early stage ER+ breast tumors that have recurred after adjuvant therapy, including patients with late relapse, early relapse, and no relapse at 10 years. IRB approval was obtained to obtain and sequence these samples, and approval from the DFCI Breast Cancer User Committee for use of these tissues was also obtained. Due to delays in the sequencing platform development, user committee approval, and limitations of funding sources to perform the sequencing on all 150 samples, this aim has not yet been completed. Additional funding sources are presently being obtained, and, once funding is in place, sequencing is expected to be completed by the end of the grant term in December 2015.

TASKS (WITH REVISED TIMELINE):

- Sample collection completed: *September 2015*
- DNA extraction, quantitation, and library construction completed: *October 2015*
- Targeted massively parallel sequencing completed: *December 2015*
- Analysis of sequencing data: *February 2016*
- Validation of alterations: *March 2016*
- Statistical analysis: *June 2016*

REVISED MILESTONES:

- All samples collected by *September 2015*
- All sequencing completed by *December 2015*
- Statistical analysis completed by *June 2016*

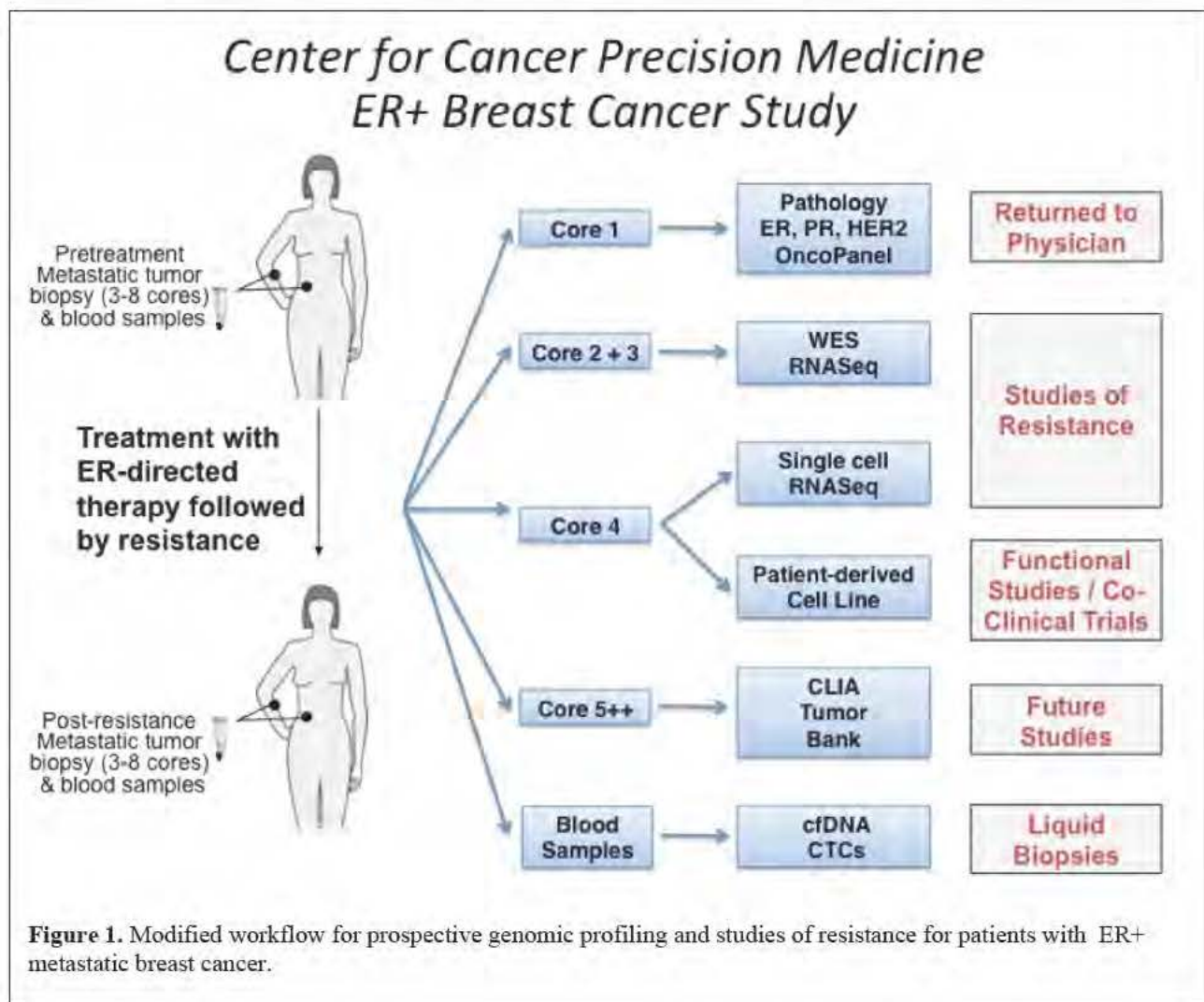
AIM #2: To assess the feasibility of prospective sequencing in patients with advanced breast cancer

In this Aim, we proposed to apply massively parallel sequencing to patients with advanced breast cancer. The goal here is to study the feasibility of our approach in a setting that may ultimately inform clinical decision-making. This will serve as a proof-of-principle for how genomics could be used prospectively for cancer precision medicine – to uncover somatic genetic changes that impact the treatment and prognosis of patients with breast cancer. Because of the delay in implementing the new targeted sequencing platform, we established a more comprehensive platform that incorporates *whole exome sequencing* and *transcriptome sequencing* (RNASeq) in patients with advanced breast cancer. This platform includes all targets in the v2.0 targeted sequencing panel described above, but is more comprehensive in that it can detect mutations, insertions/deletions, copy number alterations, and translocations in all genes in the genome, as well as genome-wide expression.

Towards the beginning of the grant term, we established a pipeline for **prospective whole exome sequencing** from FFPE tumor samples to support clinical decision making (and clinical trial enrollment) for appropriately consented patients with advanced cancers at the Dana-Farber Cancer Institute (DFCI) known as **CanSeq**. We initially conducted a pilot study on 16 patients that enabled optimization of various aspects of our emerging clinical sequencing pipeline, including sample acquisition, DNA extraction, sequencing, and analysis. The somatic and germline alterations were analyzed using a heuristic algorithm called PHIAL. This algorithm

applies a categorization framework that incorporates the degree of actionability and level of evidence for that action. A similar algorithm was also been developed for germline alterations. We also developed a customized report that streamlines the results of these algorithms for presentation to a Cancer Genomics Evaluation Committee, a multi-disciplinary “genomics tumor board” whose purpose was to make decisions about the interpretation and clinical actionability of somatic and germline alterations. Somatic analysis of the first 16 patients demonstrated at least one plausibly actionable somatic alteration linked to an approved or experimental therapy in 15 out of 16 cases. This work was published in Nature Medicine in 2014 (Van Allen, Wagle, et al, 2014).

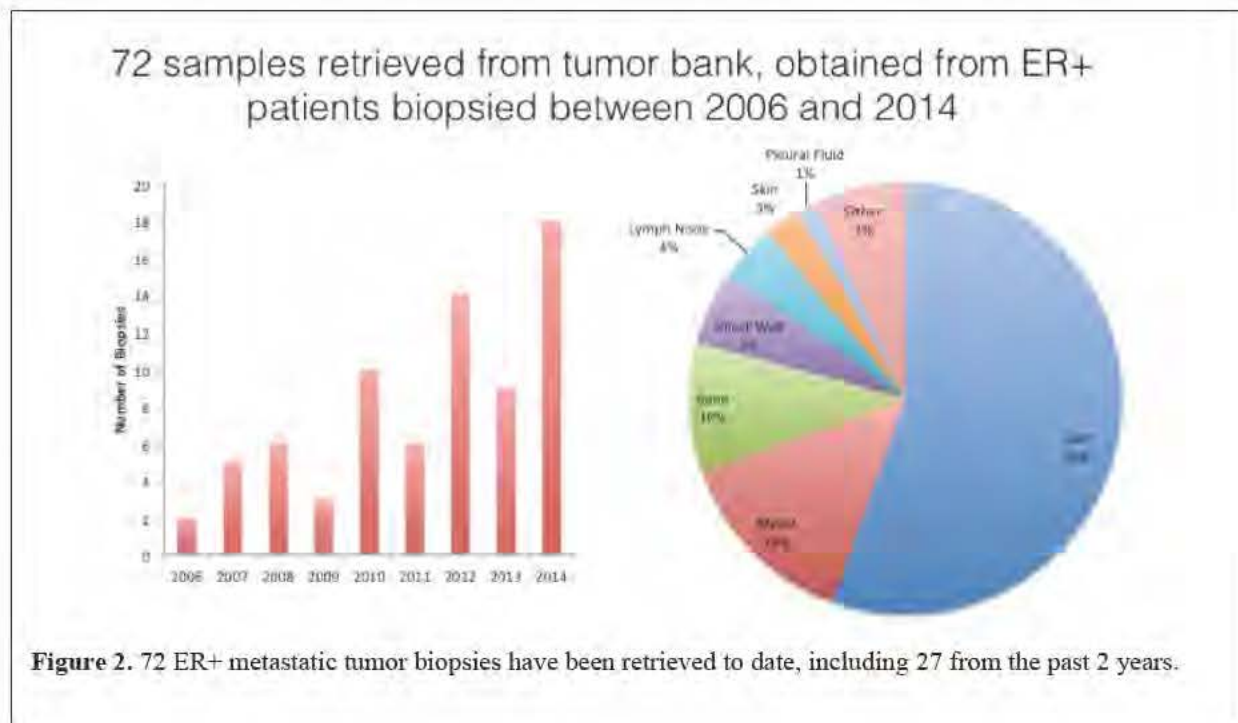
Building on the foundation established by CanSeq, our prospective sequencing approach for patients with metastatic breast cancer has continued to evolve over the past few years. Patients at DFCI with metastatic ER+ breast cancer are asked to enroll on an IRB-approved metastatic breast cancer biopsy protocol (#05-246). Under this protocol, 3-6 frozen core biopsies are collected from metastatic lesions and are available for genomic testing. For all patients, we simultaneously obtain a tube of blood as a source of germline DNA. Thus, this protocol allows prospective whole exome and transcriptome sequencing of metastatic biopsies from patients with advanced ER+ breast cancer – both for retrospective analysis and prospective return of results, when appropriate.



In 2014, during the course of this award, I transitioned from a post-doctoral fellow in Levi Garraway's laboratory to an independent faculty member in the Department of Medical Oncology at Dana-Farber Cancer Institute. In this new independent faculty role, I am a member of the new Dana-Farber/Brigham and Women's/Broad Institute Center for Cancer Precision Medicine (CCPM). As part of the CCPM, I have developed a novel infrastructure and workflow to conduct this research project, based on the experiences gained over the past few years. This is detailed in **Figure 1**. This workflow enables the acquisition of multiple clinical and research biopsies from patients with metastatic breast cancer with the return of relevant clinical information (including genomic sequencing) to the clinician and patient. The remaining tissues are available for genomic and molecular analyses, as shown in Figure 1. In this way, this new workflow serves both Aim 2A and 2B. Prospective enrollment using this new workflow began in June 2015. We anticipate enrolling approximately 3-4 patients per month on this protocol, for a total of 18-24 additional patients over the remainder of the grant term.

AIM 2A: To assess the clinical impact of prospective genomic profiling in advanced breast cancer

Under the original 05-246 protocol, we collected 72 metastatic tumor biopsies and matched blood samples from patients between 2006 and 2014, including 27 biopsies that have been collected since the start of this grant term (**Figure 2**). Whole exome and whole transcriptome sequencing of all tissues from the first 40 patients has been completed, and analysis of this data is currently underway. Sequencing from the remaining 32 patients is also currently in progress. In addition, 3-4 additional patients per month will be biopsied for the remainder of the grant term using the new Center for Cancer Precision Medicine workflow, as described above (**Figure 1**). Analysis of the entire cohort of ~100 patients is expected to be completed by the end of the grant term.

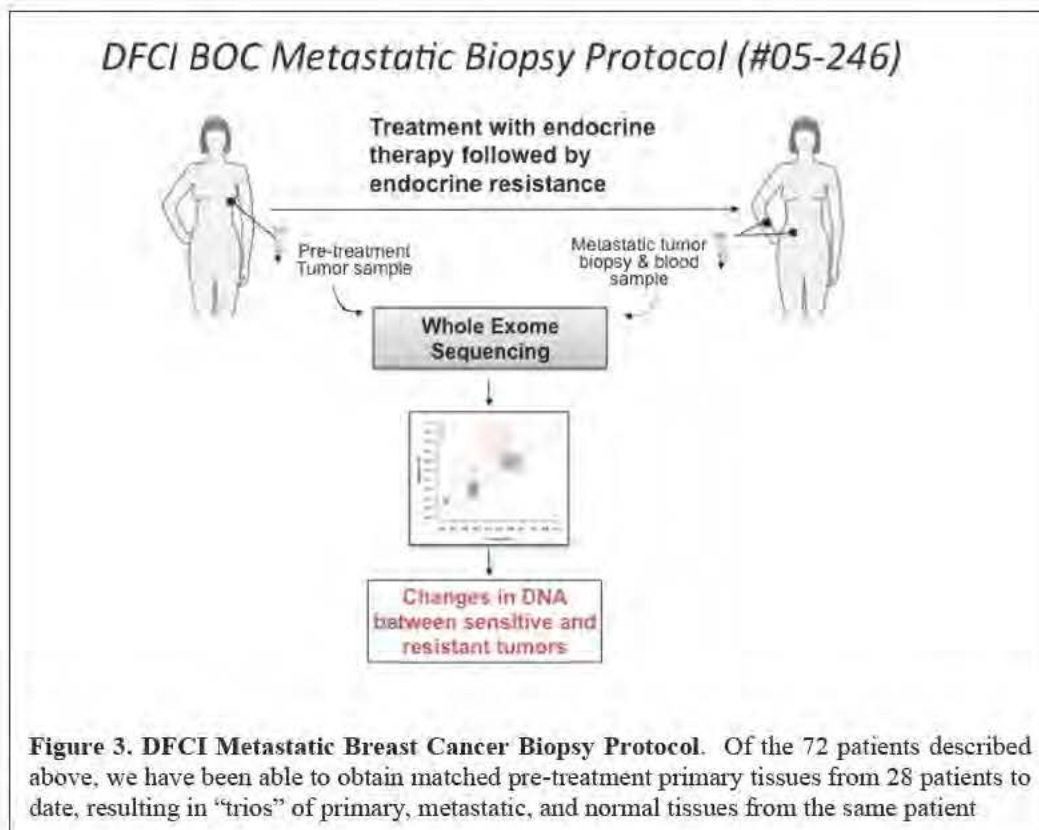


TASKS:

- Protocol activation (Month 1 – Month 3): **COMPLETE**
- Patient enrollment (Month 4 – Month 36): **ONGOING**
- Sample acquisition (Month 4 – Month 36): **ONGOING**
- Genomic profiling (including DNA extraction, library construction, sequencing, and validation) (Month 4 – Month 36): **ONGOING**
- Interpretation of genomic alterations and reporting to physicians/patients (Month 4 – Month 36): **ONGOING**
- Analysis of feasibility and clinical impact (Month 4 – Month 36): **ONGOING**

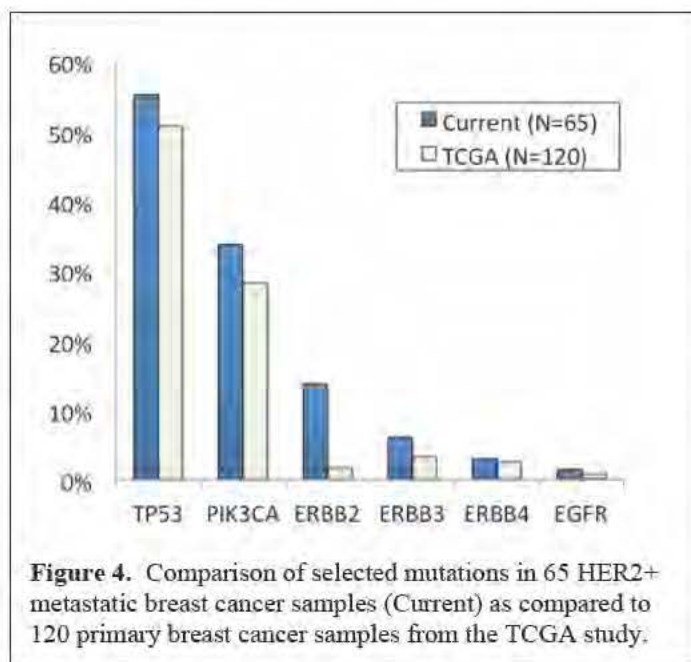
MILESTONES:

- Protocol activated and patient enrollment begins by *Month 4*: **COMPLETE**
- Sequencing of first 5-10 patients completed and reported to physician/patient by *Month 9*: **COMPLETE**
- Analysis of feasibility and clinical impact of first 5-10 patients by *Month 12*: **COMPLETE**
- Sequencing of first 20 patients completed and reported to physician/patient by *Month 18*: **COMPLETE**
- Analysis of feasibility and clinical impact of first 20 patients by *Month 21*: **ONGOING**
- Sequencing of at least 50 patients completed and reported to physician by *Month 33*
- Analysis of feasibility and clinical impact of 50 patients by *Month 36*



AIM 2B: To use whole-exome sequencing to identify genomic mechanisms of therapeutic resistance

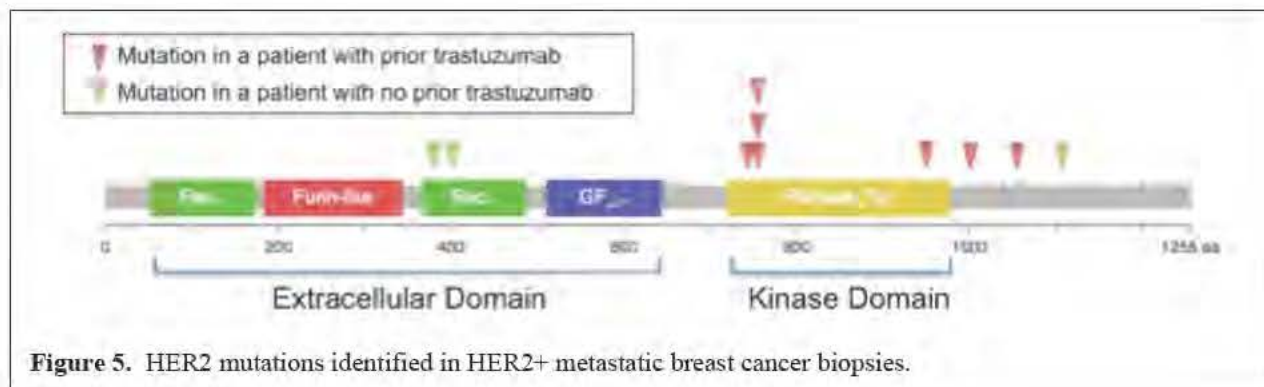
The goal of this aim is perform whole exome sequencing in breast cancer patients who develop resistance to targeted therapies (e.g., endocrine therapies, anti-Her2 therapies, PI3K inhibitors, mTOR inhibitors) in order to identify novel resistance mechanisms. Of the 72 patients described above, we have been able to obtain matched pre-treatment primary tissues from 28 patients, resulting in 28 “trios” of primary, metastatic, and normal tissues from the same patient (**Figure 3**). Sequencing of these trios has now been completed, and analysis is underway. We are also in the process of obtaining and sequencing the pretreatment samples from the remaining patients, and expect to have pre-treatment and post-resistance analysis on at least 50 patients with ER+ metastatic breast cancer by the end of the grant term.



In addition, we had access to metastatic tumor biopsies collected from patients enrolled on a phase II study evaluating the combination of lapatinib and trastuzumab in patients with metastatic HER2+ breast cancer. The total study accrual was 116 patients and a baseline tumor biopsy was required at time of study entry. By design, patients had varying degrees of prior trastuzumab exposure. We performed deep whole exome sequencing (WES) on metastatic frozen tumors and matched normal tissue from **65 patients** plus 54 matched archival FFPE primary samples. The two most significant recurrently mutated genes in this cohort were PIK3CA (n=22; 34%) and TP53 (n=36; 55%).

As shown in **Figure 4**, compared to 120 primary, treatment-naïve HER2+ tumors sequenced in the TCGA study, there was no significant difference in the incidence of point mutations and indels in TP53 and PIK3CA (55% and 34%, respectively). However, the incidence of *ERBB2* (HER2) mutations was significantly increased (14% vs 2%, $p = 0.002$). There was no significant difference in the mutation rates in ERBB3, ERBB4, and EGFR.

HER2 mutations have previously been identified in ~2% of primary HER2- cancers and <2% of primary HER2+ cancers (CBio portal). In our study, we identified a somatic HER2 mutation in 9 out of 65 metastatic biopsies (14%), 5 of which were in the kinase domain (**Figure 5**). The HER2 L755S mutation (found in 3 patients) is a well-described activating mutation in HER2 that results in resistance to lapatinib and sensitivity to irreversible inhibitors (e.g. neratinib). The remaining 2 kinase domain mutations have not been described previously. They were present at low allelic fractions, both in patients who received prior trastuzumab. Characterization of these mutations is currently underway. 4 additional patients, 2 of whom received prior trastuzumab, had uncharacterized mutations in other domains of HER2 at low allelic fractions



Additional recurrently mutated genes occur at much lower frequencies and are being confirmed. In addition, an analysis to identify genes that may contribute to resistance to trastuzumab is being conducted by comparing matched metastatic and primary biopsies from the 46 patients who received prior anti-Her2 therapy prior to the metastatic biopsy.

The results for these studies on HER2+ metastatic breast cancer patients were presented in a Poster Highlights session at the 2014 ASCO Annual Meeting (Wagle et al, 2014b) and in a Poster Highlights session with an oral presentation at the 2014 San Antonio Breast Cancer Symposium (Wagle et al, 2014b). A manuscript is currently in preparation.

TASKS:

- Whole exome sequencing of patients with acquired resistance to targeted therapies (Month 9 – Month 36): **COMPLETE**

MILESTONES:

- Whole exome sequencing on first 3-6 patients with acquired resistance completed by **Month 16: COMPLETE**
- Whole exome sequencing of at least 15 patients with acquired resistance completed by **Month 33: COMPLETE**

4. KEY RESEARCH ACCOMPLISHMENTS:

- Development of a novel targeted sequencing platform that includes ~450 genes that are significantly altered in breast cancer and other cancers, including novel unpublished alterations that we have recently identified in ER+ breast cancers
- Development of a prospective whole exome sequencing pipeline (CanSeq) that includes sequencing from FFPE samples, analysis, curation, and interpretation of clinically relevant somatic and germline alterations, discussion of key findings by the Cancer Genome Evaluation Committee, and return of results to physicians and patient (Van Allen, Wagle, et al, Nature Medicine, 2014)
- Implementation of a novel Cancer Precision Medicine infrastructure and workflow that involves the acquisition of metastatic research biopsies with triage of samples for clinical pathology and receptor testing, clinical targeted sequencing (with return of

results), whole exome and transcriptome sequencing, single cell transcriptome sequencing, and cell line generation, as well as circulating tumor cell analysis and cell free DNA analysis. The initial patient to utilize this workflow was biopsied in June 2015.

- Whole exome sequencing of 65 HER2+ metastatic breast cancer, the largest such cohort described to date. Sequencing analysis has demonstrated:
 - PIK3CA and TP53 were significantly recurrently mutated in these tumors, at the same rate as in primary, treatment-naïve HER2+ breast cancer
 - The prevalence of PIK3CA and TP53 mutations was similar in the metastatic samples from those patients who received prior trastuzumab and those who were trastuzumab naïve, though some metastatic biopsies in patients who received prior trastuzumab had mutations of interest not detected in the corresponding primaries
 - Somatic HER2 mutations in patients with HER2+ MBC treated seem to occur at a higher rate than in primary HER2+ breast cancer, and may be involved in resistance to trastuzumab and lapatinib

5. CONCLUSION:

To date, we have made significant progress on this research project. Given the progress to date, we anticipate that we will achieve our stated research goals by the end of the grant term. For Aim 1, to accomplish this, we will utilize the targeted sequencing panel we have developed to profile 150 early stage ER+ breast cancers, as we have described. For Aim 2, we will continue to perform whole exome and targeted sequencing on patients with advanced breast cancer until we reach our stated goal of 50 patients. This will likely be completed in several months. Although Aim 2B has largely been completed, we will continue to perform additional sequencing to compare resistant tumors to their pre-treatment sensitive tumor, as we have demonstrated for many patients already.

Once successfully completed, this work should provide new knowledge that informs the development of novel treatment strategies in breast cancer. These include treatments that may prevent early and/or late recurrence in ER+ breast cancers, new approaches to determining how best to use targeted therapies in advanced breast cancer, and novel strategies to overcome resistance mechanisms. If widely deployed, implementation of this approach may open new opportunities to link cancer genomics with molecular features, clinical outcomes, and treatment response in patients with breast cancer. This approach may ultimately impact clinical practice by offering a categorical means to identify genetic changes affecting genes and pathways targeted by existing and emerging drugs, thereby speeding the advent of personalized cancer medicine.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. Manuscripts:

(1) Lay Press:

None

(2) Peer-Reviewed Scientific Journals:

Van Allen EM*, **Wagle N***, Stojanov P, Perrin DL, Cibulskis K, Marlow S, Jane-Valbuena J, Friedrich DC, Kryukov G, Carter SL, McKenna A, Sivachenko A, Kiezun A, Voet D, Lawrence M, Lichtenstein LT, Gentry JG, Huang FW, Farlow D, Barbie D, Gandhi L, Lander ES, Gray SW, Joffe S, Janne P, Garber J, MacConaill L, Lindeman N, Rollins B, Kantoff P, Fisher SA, Gabriel S, Getz G, and Garraway LA. Whole- exome sequencing and clinical interpretation of FFPE tumor samples to guide precision cancer medicine. *Nature Medicine*. 2014 Jun;20(6):682-8. Epub 2014 May 18.
(*Dual-First Author)

(3) Invited Articles:

Stover DG and **Wagle N***. Precision medicine in breast cancer: genes, genomes, and the future of genomically driven treatments. *Curr Oncol Rep*. 2015 Apr;17(4):438.
(*Corresponding Author)

(4) Abstracts:

1. **Wagle N***, Van Allen EM*, Frederick DT, Cooper ZA, Farlow DN, Treacy D, Goetz EM, Johannessen CM, Carter SL, Taylor-Weiner A, Hodis E, Lawrence DP, Sullivan RJ, Getz G, Gabriel SB, Flaherty K, Wargo JA, and Garraway LA. Whole exome and whole transcriptome sequencing in melanoma patients to identify mechanisms of resistance to combined RAF/MEK inhibition. 2013 ASCO Annual Meeting, Chicago, IL, May 31- June 4, 2013. [Poster Discussion]
2. **Wagle N**, Van Allen E, Perrin D, Friedrich D, Fisher S, Kryukov G, Ambrogio L, Auclair D, Gray S, Joffe S, Janne P, Garber J, Macconail L, Lindeman N, Rollins B, Kantoff P, Getz G, Gabriel S, and Garraway LA. CanSeq: prospective clinical whole-exome sequencing of FFPE tumor samples. 104th American Association for Cancer Research Annual Meeting, Washington, DC, April 6-10, 2013.
3. Van Allen EM, **Wagle N**, Keizun A, Kryukov G, McKenna A, Huang F, Hiller E, Rainville I, Auclair D, Ambrogio L, Gray S, Joffe S, Getz G, Garber J, and Garraway L. An integrated germline analysis platform for comprehensive clinical cancer genomics. 104th American Association for Cancer Research Annual Meeting, Washington, DC, April 6-10, 2013.
4. Van Hummelen P, Ducar M, Jones RT, Raza A, Sunkavalli A, Hanna M, Mills A, Adusumilli R, Kumar P, Schubert L, Breneiser M, Cooley AC, Garcia E, Scholl LM, Lindeman NI, **Wagle N**, Garraway L, Cibulskis K, Carter SL, Lawrence M, Getz G, Meyerson ML, Hahn WC, and MacConaill LE. Targeted sequencing to detect somatic mutations, translocations and copy-number variation in human tumors simultaneously. 104th American Association for Cancer Research Annual Meeting, Washington, DC, April 6-10, 2013.
5. Rodon J, Juric D, Gonzalez-Angulo A, Bendell J, Berlin J, Bootle D, Gravelin K, Huang A, Derti A, Lehar J, Würthner J, Boehm M, van Allen E, **Wagle N**, Garraway LA, Yelensky R, Stephens PJ, Miller VA, Schlegel R, Quadt C, Baselga J. Towards defining the genetic

framework for clinical response to treatment with BYL719, a PI3Kalpha-specific inhibitor. 104th American Association for Cancer Research Annual Meeting, Washington, DC, April 6-10, 2013. [Oral Abstract, presented by J Rodon]

6. **Wagle N**, MacConaill LE, Garcia E, Kuo FC, Longtine JA, Garber JE, Janeway KA, Fuchs CS, Bertagnolli MM, Soiffer R, Matulonis U, Lin NU, Hahn WC, Garraway LA, Kantoff PW, Lindeman NI, and Rollins BJ. PROFILE: Broadly based genomic testing for all patients at a major cancer center. 2013 ASCO Annual Meeting, Chicago, IL, May 31- June 4, 2013. [Poster Discussion]
7. **Wagle N***, **Lin NU***, Richardson AL, Leshciner I, Mayer AI, Forero-Torres A, Hobday TJ, Dees EC, Nanda R, Rimawi, MF, Guo H, Barry WT, Wolff AC, Gabriel SB, Garraway LA, Winer EP, Krop IE, on behalf of the Translational Breast Cancer Research Consortium. Whole-exome sequencing (WES) of HER2+ metastatic breast cancer (MBC) from patients (pts) treated with prior trastuzumab (T): A correlative analysis of TBCRC003. 2014 ASCO Annual Meeting, Chicago, IL, May 30-June 3, 2014. [Poster Highlights Discussion]
8. **Wagle N***, **Lin NU***, Richardson AL, Leshciner I, Mayer AI, Forero-Torres A, Hobday TJ, Dees EC, Nanda R, Rimawi, MF, Guo H, Barry WT, Bose R, Shen W, Wolff AC, Gabriel SB, Garraway LA, Winer EP, Krop IE, on behalf of the Translational Breast Cancer Research Consortium. Whole exome sequencing (WES) of HER2+ metastatic breast cancer (MBC) from patients with or without prior trastuzumab (T): A correlative analysis of TBCRC003. 2014 San Antonio Breast Cancer Symposium. [Poster Highlights Discussion and Oral Presentation]

- b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

Local Invited Presentations

2014	“Clinical Genomics and Precision Cancer Medicine” Department of Pediatrics Hematology/Oncology Seminar Boston Children’s Hospital	Seminar
2014	“Clinical Genomics and Precision Cancer Medicine” Center for Cancer Precision Medicine Department of Medical Oncology Seminar Dana-Farber Cancer Institute	Seminar

Regional Invited Presentations and Courses

Regional

2015	“Translational Genomics and Precision Cancer Medicine” Department of Pathology Boston University School of Medicine Boston, MA	Invited Talk
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National Invited Presentations and Courses

2014	<p>“Clinical Genomics and Precision Cancer Medicine” Abramson Cancer Center University of Pennsylvania Philadelphia, PA</p>	Invited Talk
2014	<p>“Clinical Genomics and Precision Cancer Medicine” Center for Molecular Oncology Memorial Sloan-Kettering Cancer Center New York, NY</p>	Invited Talk
2014	<p>“How Can We Move Forward with Combination Targeted Therapies in a Breast Cancer Genomically-Driven Trial?” Innovations in Breast Cancer Drug Development: Next Generation Oncology Trials Breast Cancer Workshop U.S. Food and Drug Administration Washington, DC</p>	Invited Talk and Panelist
2014	<p>“Whole exome sequencing (WES) of HER2+ metastatic breast cancer (MBC) from patients with or without prior trastuzumab (T): A correlative analysis of TBCRC003” San Antonio Breast Cancer Symposium 2014, San Antonio, TX</p>	Short Talk (abstract)
2015	<p>“Assigning Clinical Meaning to Cancer Genome Data” American Association of Cancer Research Annual Meeting 2015 Washington, DC</p>	Invited Talk and Chairperson
2015	<p>“CanSeq: Whole Exome Sequencing to Guide the Care of Cancer Patients ” American Association of Cancer Research Annual Meeting 2015 Washington, DC</p>	Invited Talk and Panelist
2015	<p>“CanSeq: Whole Exome Sequencing to Guide the Care of Cancer Patients ” American Association of Cancer Research Precision Medicine Series Integrating Clinical Genomics and Cancer Therapy Salt Lake City, UT</p>	Invited Talk

International Invited Presentations and Courses

2014	<p>“Clinical Cancer Genomics and Precision Cancer Medicine” Applied Cancer Genomics Symposium Princess Margaret Cancer Center Toronto, Canada</p>	Invited Talk
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7. INVENTIONS, PATENTS AND LICENSES:

Nothing to report.

8. REPORTABLE OUTCOMES:

Nothing to report.

9. OTHER ACHIEVEMENTS:

a) Promotion to independent faculty member at Dana-Farber Cancer Institute and Harvard Medical School

In July 2014, I was appointed as an independent faculty member in Department of Medical Oncology at Dana-Farber, with my own laboratory and translational research program in breast cancer. My promotion to Assistant Professor at Harvard Medical School is currently pending. I also serves as an inaugural faculty member in the new Center for Precision Cancer Medicine at DFCI and I was appointed as an Associate Member of the Broad Institute of Harvard and MIT.

b) Over the course of this award, I have obtained several awards and grants, several of which are related to the preliminary data generated by this award (indicated with an *):

*2013 – 2015 *Systematic genomic profiling of endocrine-resistant breast cancer*
Landon Foundation-AACR INNOVATOR Award for Research in Personalized Cancer Medicine (Wagle)
Principal Investigator (\$100,000)

2014 – 2015 *Exceptional Responses in Cancer*
Next Generation Fund of the Broad Institute of Harvard and MIT (Wagle)
Principal Investigator (\$100,000)

*2014 – 2016 *Identifying resistance mechanisms in ER+ breast cancer by translational genomics*
Dana-Farber/Harvard SPORE in Breast Cancer Career Development Award (Wagle)
Principal Investigator (\$80,000)

*2015 – 2018 *Identifying resistance mechanisms in ER+ breast cancer by translational genomics*
Susan G. Komen Career Catalyst Research Grant (Wagle)
Principal Investigator (\$450,000)

10. TRAINING AND PROFESSIONAL DEVELOPMENT:

I continue to be advised by an exceptional group of mentors to help guide me in my research and my career development. My primary scientific mentor is Dr. Levi Garraway, a visionary physician-scientist with an extraordinary scientific track record who has served as an outstanding personal and professional role model. I have also continued to be mentored by a committee comprised of world-class experts in breast cancer translational research and cancer genomics,

who have provided invaluable guidance over the course of this award. My training has also been enhanced by my training environment. I have had the opportunity to attend multiple weekly and monthly seminars and courses as well as present my work in them. In addition, I have had the opportunity to attend numerous scientific meetings over the past few years, including the San Antonio Breast Cancer Symposium, the AACR Annual Meeting, the ASCO Annual Meeting, the AACR-EORTC-NCI Meeting on Molecular Targets and Cancer Therapeutics, and several meetings and workshops of the NHGRI Clinical Sequencing Exploratory Research Consortium.

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