BIOGRAPHICAL SKETCH

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NAME: Larry Norton, MD

eRA COMMONS USER NAME (credential, e.g., agency login): NORTONL

POSITION TITLE: Deputy Physician-in-Chief, Memorial Hospital, for Breast Cancer Programs

Medical Director, Evelyn H. Lauder Breast Center

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Rochester, NY	AB, Summa Cum Laude φβκ	05/1968	Psychology
College of Physicians and Surgeons, Columbia University, NY	MD, αοα	06/1972	Medicine

A. Personal Statement

Although my formal training and dominant activity is breast cancer medical oncology, particularly clinical trials, I have for more than four decades been involved in all aspects of cancer medicine including governmental and administrative roles, laboratory investigations, advocacy, education, grant making, policy making, and my particular area of research: mathematical modeling.

B. Positions and Honors

Positions and Employment

1977-1988 Mount Sinai School of Med., NY, Dept. of Neoplastic Diseases: Assistant Professor: 1988-84; Associate Professor: 1988-92

1988 - Memorial Sloan-Kettering Cancer Center, NY, Dept. Med.: Associate Member: 1988-92; Member: 1992-; Chief, Breast Cancer Medicine Service, 1989-1997; Head, Division of Solid Tumor Oncology: 1997-2003; **Deputy Physician-in-Chief, Memorial Hospital, for Breast Cancer Programs, 2003-**

1988 Weill Medical College, Cornell University, NY, Dept. Medicine: Associate Professor: 1988-92; **Professor, 1992-**

Other Experience and Professional Memberships

1980 - CALGB: Breast Cancer Core: 1980 – (Vice-chair, 1985-88; Chair, 1988-90, 1995-2003).

1985 - NCI: Cancer Clinical Investigations Review Committee: 1985-90 (Chair, 1988-90); Workshop on Predictive Markers in Clinical Cancer: 1992 (Co-Chair), Program for the Assessment of Clinical Cancer Tests: 2000-

1986-	ASCO: Foundation Chair: 2002-2004; **President: 2001-02;** Program Committee: 1986-87; Chair, Breast Cancer Subcomittee: 1992, 1996; Nominating Committee: 1989; Awards Selection Committee: 1991-94 (Chair, 1993); Board of Directors: 1996-1999.
1990	NIH: Consensus Conference Treatment Early Stage Breast Cancer.
1993	IOM, NAS: Committee to Advise Dept. Defense: 1993, Committee on Lesbian Health Priorities: 1997, Committee on Unequal Burden of Cancer: 1998, Committee on Breast Imaging Modalities: 1999-2000, Committee on New Approaches to Early Detection & Diagnosis of Breast Cancer
1993-1996	NY Dept. Health: Breast Cancer Treatment Quality Advisory Panel, 1993-1996.
1999-2004	**National Cancer Advisory Board, Member.**
2002-2005	GM Cancer Research Foundation, Member, Awards Assembly.
2002-2009	Y-ME National Breast Cancer Organization, Member, Board of Directors.
2003-	Young Survival Coalition: Medical Advisory Board.
2005-	Friends of Cancer Research: Scientific Advisory Board.
2005-	AACR: Consumer Cancer Magazine, Editorial Board Member: 2005-; Centennial Program Committee: 2006.

Honors

1968	NY State Medical Scholarship Award.
1990	B. Pfeifer Award for Scientific Excellence, American-Italian Foundation for Cancer Research.
1993	The 2nd Belsky-Moranis Lecture, NY University Medical Center.
1994	Wedgewood Award, Don Shula Foundation.
1995	Pathbreaker Award, National Alliance of Breast Cancer Organizations, New York.
1995	Distinguished Service Award, Cancer Care, Inc., New York.
1995	SHARE Breast Cancer Award, New York.
1995	First Incumbent, the Norma S. Sarofim Chair in Clinical Oncology.
1995	Biran Visiting Professorship, Hadassah University Hospital, Jerusalem.
1996	Schlager Visiting Professorship, Dana-Farber Cancer Institute, Boston.
1996	Vivian Saykaly Visiting Professorship, McGill University/Universite de Montreal, Canada
2000	8th Claude Jacquillat Award for Achievement in Clinical Oncology.
2003	Paul Carbone Visiting Professor, University of Wisconsin Comprehensive Cancer Center.
2003	FIFO Award: II Premio Internacional de Oncología Duque de Bajadoz (La Fundación para la Investigación y Formación en Oncología).
2003	Arthur G. Michel MD Award for Excellence in Breast Cancer Care, Y-ME National Breast Cancer Organization.
2004	**The David A. Karnofsky Memorial Award, American Society of Clinical Oncology.**
2004	Susan G. Komen Foundation Brinker Award for Scientific Distinction.
2005	Herbert & Maxine Block Memorial Lectureship Award for Distinguished Achievement in Cancer.
2006	The Jeffrey A. Gottlieb Memorial Award for Outstanding Achievement in Cancer Therapeutic Research.
2006	Co-Recipient, The Gilda Award for the Contribution to the Advancement of Cancer Medicine.
2006	The Annual Glenn Robbins Award presented by the New York Cancer Society and the New York Metropolitan Breast Cancer Group.
2006	**The Jill Rose Award for Distinguished Scientific Achievement, Breast Cancer Research Foundation.**
2007	The Society of Memorial Sloan-Kettering Cancer Center's Award for Excellence in Medicine.
2007	The Statesman Award, American Society of Clinical Oncology.
2007	Vivian and Meyer P. Potamkin Award, Pennsylvania Breast Cancer Coalition.
2008	**The William L. McGuire Lecture Award.**
2010	Castle Connolly Clinical Excellence Award.
2011	Hope Funds for Cancer Research Award.
2013	Recipient of the Willet F. Whitmore Award for Clinical Excellence
2013	Gianni Bonadonna Breast Cancer Award.
2014	Columbia University, Physicians and Surgeons Alumni Association's Gold Medal For Outstanding Achievement in Medical Research.

C. Contribution to Science

1. Optimizing the drug treatment of cancer requires attention to schedule as well as drug choice and dose level. My colleagues and I were the first to apply mathematical methods to this problem. (1) I was the first to describe the now universally-accepted Gompertzian pattern of growth to human breast cancer (2) and developed the theoretical basis for both sequential and dose-dense drug therapy. With colleagues we conducted a series of clinical studies that established the feasibility and non-comparative efficacy of the application of these ideas. (3) As the chair of breast cancer research in a major cooperative group (the Cancer and Leukemia Group B, CALGB) I led a definitive study that demonstrated the survival benefit of this approach. (4) A world-wide overview of all trials of this nature is soon to be published that confirms a major impact on reducing breast cancer mortality.

    1. Norton L, Simon R. Tumor size, sensitivity to therapy and the design of treatment protocols. Cancer Treat Rep. 1977 Oct; 61(7):1307-17.

    2. Norton L. A Gompertzian Model of Human Breast Cancer Growth. Cancer Res. 1988 Dec 15; 48(24 Pt 1):7067-71.

    3. Hudis C., Seidman A., Raptis G., Baselga J., Gilewski T., Fennelly D., Lebwohl D., Surbone A., Currie V., Moynahan M., Theodoulou M., Sklarin N., Uhlenhopp M., Yao T-J., Norton L. Event-free survival after sequential dose-dense doxorubicin (A), paclitaxel (T) and cyclophosphamide (C) in women (pts) with greater than or equal to 4 positive (+) axillary lymph nodes (LN). Breast Can Res Treat. 1996:41:232.

    4. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, Davidson NE, Martino S, Livingston R, Ingle JN, Perez EA, Carpenter J, Hurd D, Holland JF, Smith BL, Sartor CI, Leung EH, Abrams J, Schilsky RL, Muss HB, Norton L. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol. 2003 Apr 15; 21(8):1431-9.

2. The above achievement depended to a significant extent on the development of truly effective drugs for the treatment of breast cancer. One of the most important in this regard is paclitaxel, which we studied in MSKCC's Breast and Gynecological Cancer Medicine Service, which I led during this period. (5) We demonstrated that granulocyte colony stimulating factor (G-CSF) could be used to support paclitaxel use (6), which was a major advance that made the discovery of reference (4) possible. Furthermore, we pioneered the weekly schedule (7), which is now the most common schedule, also established during my tenure as a leader in the CALGB. We combined this result with the work I led on the development of trastuzumab (below) to create one of the most effective breast cancer therapies in use today for a targeted population (HER2 over-expressing disease). (8)

    5. Seidman AD, Hudis CA, Norton L. Memorial Sloan-Kettering Cancer Center experience with paclitaxel in the treatment of breast cancer: from advanced disease to adjuvant therapy. Semin Oncol. 1995 Aug; 22(4 Suppl 8):3-8.

    6. Reichman BS, Seidman AS, Crown JP, Heelan R, Hakes TB, Lebwohl DE, Gilewski TA, Surbone A, Currie V, Hudis CA, Yao T-J, Klecker R, Jamis-Dow C, Collins J, Quinlivan S, Berkery R, Toomasi F, Canetta R, Fisherman J, Arbuck S, Norton L. Paclitaxel and Recombinant Human Granulocyte Colony- Stimulating Factor as Initial Chemotherapy for Metastatic Breast Cancer. J Clin Oncol. 1993 Oct; 11(10):1943-51.

    7. Fennelly D, Aghajanian C, Shapiro F, O'Flaherty C, McKenzie M, O'Connor C, Tong W, Norton L, Spriggs D. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol. 1997 Jan; 15(1):187-92.

8. Seidman, A.D., Fornier M.N., Esteva F.J., Tan L., Kaptain S., Bach A., Panageas K.S., Arroyo C., Valero V., Currie V., Gilewski T., Theodoulou M., Moynahan M.E., Moasser M., Sklarin N., Dickler M., D'Andrea G., Cristofanilli M., Rivera E., Hortobagyi G.N., Norton L., Hudis C.A. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. J Clin Oncol. 2001 May 15; 19(10):2587-95.

3. The large collection of breast cancer cases with clinical follow-up and family histories at MSKCC was used during my period of leadership of the Breast Cancer Medicine Service to define the clinical significance of specific mutations in the BRCA1 gene, the dominate gene (with BRCA2) associated with hereditary susceptibility to breast and ovarian cancer. (9) We followed this work with specific attention to the Askenazi Jewish population, not only finding specific mutations that accounted for the vast majority of cases (10), but defining the prevalence and clinical significance of this finding. (11) Extensive efforts in this area have been published, including pioneering studies of risk-reducing surgery (12), which is now a standard approach based on our work.

9. Shattuck-Eidens D, McClure M, Simard J, Labrie F, Narod S, Couch F, Hoskins K, Weber B, Castilla L, Erdos M, Brody L, Friedman L, Ostermeyer E, Szabo C, King M-C, Jhanwar S, Offit K, Norton L, Gilewski T, Lubin M, Osborne M, Black D, Boyd M, Steel M, Ingles S, Haile R, Lindblom A, Olsson H, Borg A, Bishop DT, Solomon E, Radice P, Spatti G, Gayther S, Ponder B, Warren W, Stratton M, Liu Q, Fujimura F, Lewis C, Skolnick MH, Golgar DE. A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene. JAMA. 1995 Feb 15; 273(7):535-41.

10. Haas B., Forsyth I., Hochhauser D., Neuhausen S., Gilewski T., Hampel H., Brown K., Borgen P., Norton L., Offit K. Frequent occurrence of specific germline mutations of BRCA1 and BRCA2 in Ashkenazi Jewish women with breast cancer. Am J Human Gen. 1996:59:A76.

11. Robson M., Dabney M.K., Rosenthal G., Ludwig S., Seltzer M.H., Gilewski T., Haas B., Osborne M., Norton L., Gilbert F., Offit K. Prevalence of recurring BRCA mutations among Ashkenazi Jewish women with breast cancer. Genet Test. 1997; 1(1):47-51.

12. Scheuer L.M., Robson M., Baum R., Capasso M., Duteau-Buck C., Hull J., Kelly B., McDermott D., Pierce H., Pinto M., Schulz C., Barakat R., Borgen P., Hudis C., Norton L., Offit K. Risk-reducing surgery outcomes among a series of BRCA heterozygotes. Am J Human Genetics. 2000:67:429.

4. At MSKCC I was the clinical leader of the work establishing the efficacy of trastuzumab in HER-2 over-expressing breast cancer. (8, 13) In the Breast Cancer Medicine Service Drs. Baselga et al. conducted the initial phase II trial of this agent, which did demonstrate single-agent activity for the first time. (13) In the laboratory of Dr. John Mendelsohn, Dr. Baselga and I discovered the synergy between this agent and paclitaxel (14), which was important for the clinical finding in reference (8) and the definitive study of reference (15), later combined with that of reference (4) to establish the most effective adjuvant drug therapy regimen in use today for the curative treatment of HER-2 over-expressing primary breast cancer. In the CALGB during my tenure in the research leadership capacity we demonstrated that HER-2 status could be used to choose the optimal drug combinations for use in the adjuvant setting. (16)

13. Baselga J, Tripathy D, Mendelsohn J, Baughman S, Benz CC, Dantis L, Sklarin NT, Seidman A, Hudis CA, Moore J, Rosen PP, Twaddell T, Henderson IC, Norton L. Phase II study of weekly intravenous recombinant humanized anti-$p185^{HER2}$ monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol. 1996 Mar; 14(3):737-44.

14. Baselga J., Norton L., Albanell J., Kim YM. Mendelsohn J. Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. Cancer Res. 1998 Jul 1; 58(13):2825-31.

15. Slamon D.J., Leyland-Jones B., Shak S., Fuchs H., Paton V., Bajamonde A., Fleming T., Eirmann W., Wolter J., Pegram M., Baselga J., Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar 15; 344(11):783-92.

16. Hayes DF, Thor AD, Dressler LG, Weaver D, Edgerton S, Cowan D, Broadwater G, Goldstein LJ, Martino S, Ingle JN, Henderson IC, Norton L, Winer EP, Hudis CA, Ellis MJ, Berry DA; Cancer and Leukemia Group B (CALGB) Investigators. HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med. 2007 Oct 11; 357(15):1496-506

5. The work in references (1-4) demonstrated the vital importance of the growth pattern of human breast cancer, which underlies the pattern of its response to drug therapy. Based solely on biologic reasoning Dr. Joan Massague and I hypothesized an etiology for Gompertzian growth: that cancer cells released from a tumor may self-seed back again; this was proven true with my participation a few years later. (17) The clinical implications are profound and are now being pursued in many clinical studies. (18) Additional work by Dr. Swarnali Acharyya in Dr. Massague's laboratory demonstrated the importance of leukocytes in this process and in drug resistance (19), which has motivated studies of the mutational status of tumor-infiltrating leukocytes. Furthermore, seeding could explain many phenomena in drug resistance, as first pointed out in reference (20).

17. Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, Massague J. Tumor self-seeding by circulating cancer cell. Cell. 2009 Dec 24; 139(7):1315-26.

18. Comen E, Norton L, Massague J. Clinical implications of cancer self-seeding. Nat Rev Clin Oncol. 2011 Jun;8(6):369-77.

19. Acharyya S, Oskarsson T, Vanharanta S, Malladi S, Kim J, Morris PG, Manova-Todorova K, Leversha M, Hogg N, Seshan VE, Norton L, Brogi E, Massague J. A CXCL1 paracrine network links cancer chemoresistance and metastasis. Cell. 2012 Jul 6; 150 (1):165-78.

20. Gerlinger M, Norton L, Swanton C. Acquired resistance to crizotinib from a mutation in CD74-ROS1. N Engl J Med. 2013 Sep 19;369(12):1172-3.

D. Research Support

Ongoing Research Support

NIH/NCI
P01 CA94060-03 (5)
Program Project in Models of Breast Cancer
Program Director
09/01/2002 – 06/30/2019

Completed Research Support

BCRF
I3-A159, Genomic Structural Variation in Cancer Susceptibility
Co-Principal Investigator
08/01/2009 – 08/01/2011

BCRF
DNA Vaccines against Cancer and Infectious Organisms
Co-Investigator
10/01/2009 – 10/30/2010