# The Laboratory for Quantitative Medicine

Massachusetts General Hospital/Harvard Medical School James Michaelson PhD

## DATA RESOURCES AND APPLICATIONS

Databases on Patients, Mathematics of Cancer Outcome, Screening and Treatment Analysis of Medical Usage and Cost among Cancer Patients Communication of Cancer Outcome (The CancerMath.net web calculators)

#### RESEARCH SUMMARY:

For the past decade, the work of my group has been concerned with building very large databases on patients, using this information to understand disease, and especially cancer, and its treatment, using mathematics to answer practical questions about health, and building web-based tools for communicating this information to patients and medical professionals (the CancerMath.net calculators).

#### DATABASES:

We have built a number of very large databases on patients. Last June, we were tasked by the MGH Cancer Center to build a database on all of the 173,301 Massachusetts General Hospital cancer patients,167,814 of whom were diagnosed between 1968 and 2010. The database contains 559,921 pathology reports, 575,204 discharge reports, 10,938,444 encounter notes, 304,211 operative reports, 22,009,527 procedure notes, 9,159,232 radiology reports,~1,700,000 aggregated medical bills, and ~250,000 images. The database contains all-cause survival information from the Social Security Administration Death Master File (which provides information on all deaths of persons issued social security numbers since 1937), and cause-of-death information from the Massachusetts Death Certificate Database (which contains international classification of disease cause of death information on 1,984,790 people who died in the state of Massachusetts between 1970 and 2008). The database is linked to the MGH SNAPSHOT gene sequence dataset, thus providing a great wealth of genetic data on a large number of patients.

As far as we are aware, in terms of the total mass of data, this database is the largest source of clinical information on cancer in the world.

Our group also maintains a great wealth of other data on patients, including the largest multi-institutional database on the breast cancer in the world, with data on more than 33,000 breast cancer patients (and all the varieties of information noted above). We have also built a similar multi-institutional data on melanoma patients. We also possess the Van Nuys Breast Cancer breast cancer database. We also have our own MS SQL Server re-build of the SEER national database with, for example ~325,0000 breast cancer patients for who there is full tumor size and survival information. We also possess the SEER/Medicare dataset for breast cancer. Finally, we also have build a number of specialized databases, including our database on all MGH cancer patients who were treated by liver resection.

#### MEDICAL USAGE AND COST:

Over the past year, we have served on the MGH Cancer Center's lung cancer and colon cancer redesign committees, providing detailed and actionable data on medical use and cost for cancer patients. For example, our analysis of the lung cancer patients has revealed that the total cost of treating lung cancer patients at the MGH is ~\$59 million/year, but that standardization of care has the potential of saving ~\$30 million/year.

Studies are underway for generating data on treatment and cost for patients with many types of cancer.

## A MATHEMATICAL APPROACH TO CANCER LETHALITY:

We have developed a mathematical framework for comprehending cancer lethality: the binary biological model of metastasis. This mathematics has proven to provide highly specific method for estimating of the risk of death for individual breast carcinoma patients, with an accuracy of 1%, This mathematics also provide estimates of the risk of death for melanoma, renal cell carcinoma, sarcoma, and head and neck squamous cell carcinomas, and the applicability of this mathematics in analysis of survival for other cancers is under analysis. This math also provides a basis for estimating the risk of node positivity for breast carcinoma and melanoma patients, as well as providing insight into the nature of the events of spread that underlie cancer lethality, as well as providing a way to address a whole range of questions in oncology.

Our binary-biological mathematics has also formed the core of a computer simulation model of cancer screening, which has made it possible to derive biologically plausible and testable estimates of the reduction in cancer death that can be expected from screening various patients at various intervals. This work has been accompanied by a whole range of studies on the operational details of the usage of breast cancer screening.

Our binary-biological mathematics has been used to create a series of web-based CancerMath.net calculators, which provide patients with breast carcinoma, melanoma, and renal cell carcinoma with information on their likely outcomes. For breast carcinoma, we also provide a CancerMath web-calculator that shows the benefit that they can expect from the various adjuvant chemotherapy agents available to them. Analysis of the use of these CancerMath.net calculators has taught us that they are very widely used, being consulted by 1-in-5 USA breast carcinoma patients, 1-in-2 renal cell carcinoma patients, and a large number of melanoma patients. More details can be found below.

#### CANCERMATH.net Calculators

For the last decade, my research has concerned the development of a mathematical framework for predicting survival for cancer patients, together with the impact that various treatment choices will have on that outcome and the creation of very large databases on patients so that this mathematics can be accurate.

One of the applications of this work has been the creation of a series of Cancer Math.net web calculators, which appear to have become the most widely used decision aids used by cancer patients (www.CancerMath.net). These calculators are used by ~1-in-5 breast carcinoma patients, ~1-in-2 renal cell carcinoma patients. and large numbers of patients with other cancers. This has happened quite spontaneously, without publicizing these tools.

The goal of this work has been to provide patients and their physicians with highly accurate, disinterested, information on their survival expectations, together with information on the impact that can expected from the various treatment options that are available to them.

This math also has applications in other fields, such as: generating accurate estimates of the benefit of cancer screening; generating accurate estimates of life expectancy for the insurance industry; generating accurate estimates for legal professionals of the harm caused (if any) in the detection and treatment of cancer.

We have also created a web-calculator, PreventiveMath.net (www.PreventiveMath.net), which provides individuals with a list of the class A US Preventive Services Task Force recommendations, prioritized by the benefit that they can expect, so that people can see the benefit, and choose those steps that will give them the greatest possible extension in life.

The current tools available at CancerMath.net website include:

1) Breast Cancer Outcome Calculator (Provides information on survival expectation [see below for definition\*], at the time of diagnosis, assuming standard of care therapy)

2) Breast Cancer Therapy Calculator (Provides information on survival expectation\*, and the impact which various adjuvant chemotherapy options can be expected to have on that outcome)

3) Breast Cancer Conditional Survival Calculator (Provides information on survival expectation\*, assuming standard of care therapy, for patients who have remained disease free 2-15 years after diagnosis)

4) Breast Cancer Nodal Status Calculator (Provides information on the likelihood of cancer spread to the local lymph nodes)

5) Breast Cancer Nipple Involvement Calculator Calculator (Provides information to the surgeon on the likelihood that nipple sparing surgery can be carried out without leaving cancer behind)

6) Melanoma Outcome Calculator (Provides information on survival expectation\*, at the time of diagnosis, assuming standard of care therapy) (Also includes Conditional Survival Information)

7) Renal Cell Carcinoma Outcome Calculator (Provides information on survival expectation\*, at the time of diagnosis, assuming standard of care therapy) (Also includes Conditional Survival Information)

8) Colon Cancer Cancer Outcome Calculator (Provides information on survival expectation\*, at the time of diagnosis, assuming standard of care therapy) (Also includes Conditional Survival Information)

9) Head & Neck Cancer Outcome Calculator (Provides information on survival expectation\*, at the time of diagnosis, assuming standard of care therapy) (Also includes Conditional Survival Information)

10) Sarcoma Outcome Calculator (Provides information on survival expectation\*, at the time of diagnosis, assuming standard of care therapy) (Also includes Conditional Survival Information) (completed, but not yet been posted, but viewable at the hidden link: //www.lifemath.net/cancer/sarcoma/outcome/index.php).

Notes:

1) \* survival expectation measures provided by the CancerMath calculators are: risk of death, for each of the first 15 years after diagnosis: 1) to cancer; 2) to causes of death other than cancer; 3) to all causes.

2) The outcome calculators also provide Cancer Stage.

Also provided is the life expectancy with cancer, life expectancy without cancer, and the reduction in life expectancy that is caused by cancer.

For the therapy calculator, the impact of the various breast cancer adjuvant chemotherapy regimens on these measures are given.

## **References**

- 1. Michaelson, J, Halpern, E, Kopans, D. A Computer Simulation Method For Estimating The Optimal Intervals For Breast Cancer Screening. *Radiology*. 212:551-560 1999
- 2. Michaelson, JS, Kopans, DB, Cady, B. The Breast Cancer Screening Interval is Important. Cancer 2000 88:1282-1284
- 3. Michaelson JS Using Information on Breast Cancer Growth, Spread, and Detectability to Find the Best Ways To Use Screening to Reduce Breast Cancer Death *Woman's Imaging* 3:54-57 2001
- Michaelson JS Satija S Moore R Weber G Garland G Kopans DB, Observations on Invasive Breast Cancers Diagnosed in a Service Screening and Diagnostic Breast Imaging Program *Journal of Woman's Imaging* 3:99-104 2001
- 5. Michaelson JS Satija S, Moore R Weber G Garland G Phuri, D. Kopans DB The Pattern of Breast Cancer Screening Utilization and its Consequences CANCER 94:37-43 2002
- 6. Michaelson JS Silverstein M, Wyatt J Weber G Moore R Kopans DB, Hughes, K. Predicting the survival of patients with breast carcinoma using tumor size CANCER 95: 713-723 2002
- 7. Beckett JR, Kotre CJ, Michaelson JS Analysis of benefit:risk ratio and mortality reduction for the UK Breast Screening Programme. *Br J Radiol* 76:309-20 2003
- 8. Michaelson JS Satija S, Moore R Weber G Garland G Kopans DB Estimates of the Breast Cancer Growth Rate and Sojourn Time from Screening Database Information *Journal of Women's Imaging* 5:3-10 2003
- 9. Michaelson JS Satija S, Moore R Weber G Garland G Kopans DB, Hughes, K. Estimates of the Sizes at which Breast Cancers Become Detectable on Mammographic and on Clinical Grounds *Journal of Women's Imaging* 5:10-19 2003
- 10. del Carmen MG, Hughes KS, Halpern E, Rafferty E, Kopans D, Parisky YR, Sardi A, Esserman L, Rust S, Michaelson J Racial differences in mammographic breast density. *CANCER* 98:590-6 2003
- 11. Michaelson JS, Satija S, Kopans DB, Moore RA, Silverstein, M, Comegno A, Hughes K, Taghian A, Powell S, Smith, B Gauging the Impact of Breast Cancer Screening, in Terms of Tumor Size and Death Rate *Cancer* 98:2114-24 2003
- 12. Michaelson JS, Silverstein M, Sgroi D, Cheongsiatmoy JA, Taghian A, Powell S, Hughes K, Comegno A, Tanabe KK, Smith B The effect of tumor size and lymph node status on breast carcinoma lethality. *CANCER* 98:2133-43 2003
- 13. Chen Y, Taghian A, Goldberg S, Assaad S, Abi Raad R, Michaelson J, Powell S Influence of margin status and tumor bed boost dose on local recurrence rate in breast-conserving therapy: does a higher radiation dose to the tumor bed overcome the effect of close or positive margin status in breast-conserving therapy? Int J Radiat Oncol Biol Phys 57:S358 2003
- Jagsi R, Powell S, Raad RA, Goldberg S, Michaelson J, Taghian A Loco-regional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy alone: implications for postmastectomy radiation. *Int J Radiat Oncol Biol Phys* 57:S128-9 2003
- Blanchard K, Weissman J, MoyB, PuriD, Kopans D,, , Kaine E, MooreR, Halpern E, Hughes K, Tanabe K, Smith B Michaelson J, Mammographic screening: Patterns of use and estimated impact on breast carcinoma survival Cancer 101, 495-507 2004
- 16. Ma XJ, Wang Z, Ryan PD, Isakoff SJ, Barmettler A, Fuller A, Muir B, Mohapatra G, Salunga R, Tuggle JT, Tran Y, Tran D, Tassin A, Amon P, Wang W, Wang W, Enright E, Stecker K, Estepa-Sabal E, Smith B, Younger J, Balis U, Michaelson J, Bhan A, Habin K, Baer TM, Brugge J, Haber DA, Erlander MG, Sgroi DC. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. *Cancer Cell*. 2004 Jun;5(6):607-16.
- Jones JL, Hughes KS, Kopans DB, Moore RH, Howard-McNatt M, Hughes SS, Lee NY, Roche CA, Siegel N, Gadd MA, Smith BL, Michaelson JS. Evaluation of hereditary risk in a mammography population. *Clin Breast Cancer*. 2005 Apr;6(1):38-44.
- Colbert, J Bigby JA, Smith D, Moore R, Rafferty E, Georgian-Smith D, D'Alessandro HA, Yeh E, Kopans DB, Halpern E, Hughes K, Smith BL, Tanabe KK, Michaelson J. The Age at Which Women Begin Mammographic Screening. *CANCER*: 101, 1850-1859
- 19. Blanchard K, Colbert J, Kopans D, Moore R, Halpern E, Hughes K, Tanabe K, Smith BL, Michaelson JS. The Risk of False Positive Screening Mammograms, as a Function of Screening Usage. *RADIOLOGY*, 240: 335 342 2006
- 20. Jagsi R, Raad RA, Goldberg S, Sullivan T, Michaelson J, Powell SN, Taghian AG. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int J Radiat Oncol Biol Phys.* 2005 Jul 15;62(4):1035-9.
- Dominguez FJ, Jones JL, Zabicki K, Smith BL, Gadd MA, Specht M, Kopans DB, Moore RH, Michaelson JS, Hughes KS. Prevalence of hereditary breast/ovarian carcinoma risk in patients with a personal history of breast or ovarian carcinoma in a mammography population. *Cancer*. 2005 Nov 1;104(9):1849-53.
- 22. Livestro DP, Muzikansky A, Kaine EM, Flotte TJ, Sober AJ, Mihm MC Jr, Michaelson JS, Cosimi AB, Tanabe KK. A Case-Control Study of Desmoplastic Melanoma *J Clin Oncol.* 2005 Sep 20;23(27):6739-46.
- 23. Michaelson JS, Cheongsiatmoy JA Dewey F, Silverstein M, Sgroi D Smith B. Tanabe KK, The Spread of Human Cancer Cells Occurs with Probabilities Indicative of A Non Genetic Mechanism *British Journal of Cancer* 93:1244-1249 2005

- Zabicki K, Colbert JA, Dominguez FJ, Gadd MA, Hughes KS, Jones JL, Specht MC, Michaelson JS, Smith BL. Breast cancer diagnosis in women < or = 40 versus 50 to 60 years: increasing size and stage disparity compared with older women over time. *Ann Surg Oncol.* 2006 Aug;13(8):1072-7
- 25. Rusby JE, Brachtel EF, Michaelson JS, Koerner FC, Smith BL. Breast Duct Anatomy in the Human Nipple: Three-Dimensional Patterns and Clinical Implications *Breast Cancer Research and Treatment* Jan 2007
- Livestro DP, Kaine EM, Michaelson JS, Mihm MC, Haluska FC, Muzikansky A, Sober AJ, Tanabe KK, M.D. Melanoma of the young: differences and similarities with adult melanoma, a case-matched controlled analysis *Cancer* Aug 1;110(3):614-24 2007
- 27. Pawlik TM, Gleisner AL, Bauer TW, Adams RB, Reddy SK, Clary BM, Martin RC, Scoggins CR, Tanabe KK, Michaelson JS, Kooby DA, Staley CA, Schulick RD, Vauthey JN, Abdalla EK, Curley SA, Choti MA, Elias D. Liver-Directed Surgery for Metastatic Squamous Cell Carcinoma to the Liver: Results of a Multi-Center Analysis. Ann Surg Oncol. Jun 6 2007
- 28. Virani S, Michaelson JS, Hutter MM, Lancaster RT, Warshaw AL, Henderson WG, Khuri SF, Tanabe KK. Morbidity and mortality after liver resection: results of the patient safety in surgery study. *J Am Coll Surg.* Jun;204(6):1284-92 2007.
- 29. Michaelson J, Reducing Delay in the Detection and Treatment of Breast Cancer. Adv Imag Onc In 2007
- 30. Michaelson J, Mammographic Screening: Impact on Survival in CANCER IMAGING Ed: M.A. Hayat in 2007
- 31. Dominguez FJ, Golshan M, Black DM, Hughes KS,Gadd MA, Christian R, Lesnikoski B, Specht M, Michselson JS, Smith BL Sentinel Node Biopsy is Important in Mastectomy for Ductal Carcinoma in Situ Ann Surgical Oncology 2008 Jan;15(1):268-73.
- 32. Rusby JE, Kirstein LJ, Brachtel EF, Michaelson JS, Koerner FC, Smith BL Nipple-sparing mastectomy: Lessons from ex-vivo procedures *The Breast Journal*. 2008 Sep-Oct;14(5):464-70
- 33. Rusby JE, Brachtel EF, Taghian AG, Michaelson JS, Koerner FC, Smith BL. Microscopic anatomy within the nipple: Implications for nipple sparing mastectomy. American Journal of Surgery 2007 Oct;194(4):433-7
- 34. Murphy CD, Jones JL, Javid SJ, Michaelson JS, Nolan ME, Lipsitz SR, Specht MC, Lesnikoski B, Hughes KS, Gadd MA, Smith BL,Do Sentinel Node Micrometastases Predict Recurrence Risk in Ductal Carcinoma in Situ and Ductal Carcinoma in Situ with Microinvasion? American Journal of Surgery Volume 196, Issue 4, Pages 566-568 2008
- 35. Cady B, Nathan, NR, Michaelson JS, Golshan M, Smith BL, Matched Pair Analyses of Stage IV Breast Cancer With or Without Resection of Primary Breast Site J Surgical Oncology 2008 Dec;15(12):3384-95 2008
- Rusby JE, Brachtel EF, Othus M, Michaelson JS, Koerner FC and Smith BL, Development and validation of a model predictive of occult nipple involvement in women undergoing mastectomy *British Journal of Surgery* 2008; 95: 1356– 1361
- Samphao S, Wheeler AJ, Rafferty E, Michaelson JS, Specht MC, Gadd MA, Hughes KS, Smith BL. Diagnosis of breast cancer in women age 40 and younger: delays in diagnosis result from underuse of genetic testing and breast imaging. Am J Surg. 2009 Oct;198(4):538-43
- Michaelson JS, Chen LL, Silverstein M Mihm MV, Jr., Sober AJ, Tanabe KK, Smith BL, Younger J. How Cancer at The Primary Site And In The Nodes Contributes To The Risk Of Cancer Death CANCER Nov 1;115(21):5095-107 2009
- Michaelson JS, Chen LL, Silverstein M, Cheongsiatmoy JA, Mihm MV, Jr., Sober AJ, Tanabe KK, Smith BL, Younger J. Why Cancer at The Primary Site And In The Nodes Contributes To The Risk Of Cancer Death CANCER Nov 1;115(21):5084-94 2009
- 40. Chen LL, Nolan, M, Silverstein M, Mihm MV, Jr., Sober AJ, Tanabe KK, Smith BL, Younger J., Michaelson JS, The Impact Of Primary Tumor Size, Nodal Status, And Other Prognostic Factors On The Risk Of Cancer Death CANCER 2Nov 1;115(21):5071-83 2009
- 41. Tanabe KK, Jara S, Michaelson J. Creating and providing predictions of melanoma outcome. Ann Surg Oncol. 2010 Aug;17(8):1981-2.
- 42. Pandalai PK, Dominguez FJ, Michaelson J, Tanabe KK. Clinical Value of Radiographic Staging in Patients Diagnosed With AJCC Stage III Melanoma. Ann Surg Oncol. 2011 Feb;18(2):506-13
- 43. Cady B, Michaelson JS Chung MA, The "Tipping Point" for breast cancer mortality decline has resulted from size reductions due to mammographic screening Annals of Surgical Oncology in Press 2011
- 44. Bush D, Smith B, Younger J, Michaelson JS. The non-breast-cancer death rate among breast cancer patients. Breast Cancer Res Treat. 2010 Oct 7
- 45. Michaelson JS, Chen L, Bush D, Smith B, Younger J, Improved web-based calculators for predicting breast carcinoma outcomes. Breast Cancer Res Treat. In Press 2011
- 46. Emmons KM, Cleghorn D, Tellez T, Greaney ML, Sprunck KM, Bastani R, Battaglia T, Michaelson JS, Puleo E. Prevalence and implications of multiple cancer screening needs among Hispanic community health center patients. Cancer Causes Control. 2011 011 Sep;22(9):1343-9
- 47. Michaelson JS, Chen LL, Bush D, Fong A, Smith B, Younger J. Improved web-based calculators for predicting breast carcinoma outcomes. Breast Cancer Res Treat. 2011 Aug;128(3):827-35

- Barnes JA, Lacasce AS, Feng Y, Toomey CE, Neuberg D, Michaelson JS, Hochberg EP, Abramson JS. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol. 2011 Aug;22(8):1859-64. Epub 2011 Feb 21.
- 49. Rich, S, Ali S Calkins, J, Michaelson J. Survival trends in childhood hematological malignancies Int. J. Biomath.B 05, 1250053 (2012)
- 50. Wender R, Fontham ET, Barrera E Jr, Colditz GA, Church TR, Ettinger DS, Etzioni R, Flowers CR, Scott Gazelle G, Kelsey DK, Lamonte SJ, Michaelson JS, Oeffinger KC, Shih YC, Sullivan DC, Travis W, Walter L, Wolf AM, Brawley OW, Smith RA American Cancer Society lung cancer screening guidelines.CA Cancer J Clin. 2013 Jan 11.
- Valsangkar NP, Bush DM, Michaelson JS, Ferrone CR, Wargo JA, Lillemoe KD, Fernández-Del Castillo C, Warshaw AL, Thayer SP. The Effect of Lymph Node Number on Accurate Survival Prediction in Pancreatic Ductal Adenocarcinoma. J Gastrointest Surg. 2013 Feb;17(2):257-66.

## Laboratory of Quantitative Medicine Technical Reports

(Available at http://www.lifemath.net/cancer/about/techreports/index.php)

- 1. Technical Report #1 Mathematical Methods (March 9, 2009)
- 2. Technical Report #2 Equation Parameters (March 9, 2009)
- 3. Technical Report #3 Validation: SizeOnly Equation (June 24, 2008)
- 4. Technical Report #4 Validation: Size+Nodes Equation (June 26, 2008)
- 5. Technical Report #5 Validation: Size+Nodes+PrognosticFactors Equation (July 3, 2008)
- 6. Technical Report #6 Comparisons with AdjuvantOnline (July 7, 2008)
- 7. Technical Report #7a Partners Breast Cancer Database (May 12, 2008)
- 8. Technical Report #7b SEER Breast Cancer Database (May 12, 2008)
- 9. Technical Report #8 How and Why Primary Tumor Size, Nodal Status, and Other Prognostic Factors Contribute to the Risk of Cancer Death (March 9, 2009)
- 10. Technical Report #9 Adjuvant Multi-agent Chemotherapy and Tamoxifen Usage Trends for Breast Cancer in the United States (March 27, 2009)
- 11. Technical Report #10 How the CancerMath.net Breast Cancer Calculators Work (April 6, 2009, Updated Nov 28 2009)
- 12. Technical Report #11 Comparative Effectiveness Calculators For Predicting Melanoma Death (August 19, 2009)
- 13. Technical Report #12 Accuracy of the CancerMath.net Breast Cancer Calculators over 15 years following diagnosis (August 27, 2009)
- 14. Technical Report #12b Accuracy of the CancerMath.net Breast Cancer Calculators (version 2) over 15 years following diagnosis (August 29, 2009)
- Technical Report #13 Computer Simulation Estimation of the Impact of Various Breast Cancer Screening Intervals in Women of Various Ages (April 5, 2009)
- 16. Technical Report #14 Computer Simulation Estimation of the Benefits and Costs of Breast Cancer Chemoprevention (April 5, 2009)