

Anthony John Iafrate, M.D., Ph.D.



Current Positions: Associate Pathologist
Massachusetts General Hospital
Associate Professor of Pathology
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EDUCATION

1991	B.A.	Molecular Biochemistry and Biophysics / Italian Studies	Yale University, New Haven, CT
1998	Ph.D.	Molecular Microbiology	Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
2000	M.D.	Medicine	State University of New York at Stony Brook, Stony Brook, NY

FACULTY ACADEMIC APPOINTMENTS

2005-2007	Instructor	Department of Pathology	Harvard Medical School
2007-2010	Assistant Professor	Department of Pathology	Harvard Medical School
2010-	Associate Professor	Department of Pathology	Harvard Medical School

APPOINTMENTS AT HOSPITALS/AFFILIATED INSTITUTIONS

2005-	Assistant Pathologist	Department of Pathology	Massachusetts General Hospital
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MAJOR ADMINISTRATIVE LEADERSHIP POSITIONS (Current)

2005-	Director of Diagnostic Molecular Pathology Laboratory	Department of Pathology, Massachusetts General Hospital
2007-	Executive Director, Cancer Center-Pathology Translational Research Laboratory	Massachusetts General Hospital
2010-	Genomics committee co-chair; Lung Cancer Mutation Consortium	NIH Grand Opportunity Grant; multicenter lung cancer genotyping consortium.

COMMITTEE SERVICE (Current)

2005-	Molecular Genetic Pathology Fellowship steering committee	Harvard-wide pathology training program
2007-	Institutional Review Board committee D	Dana Farber/ Harvard Cancer Center
2008-	Clinical Services Oversight Committee	Department of Pathology, Massachusetts General Hospital

PROFESSIONAL SOCIETIES

2003	American Society of Human Genetics
2003	Association for Molecular Pathology

EDITORIAL ACTIVITIES

Ad Hoc Reviewer: Journal of Neuropathology and Exp. Neurology, Journal of Molecular Diagnostics, Archives of Pathology and Laboratory Medicine, American Journal of Surgical Pathology, Expert Opinion on Medical Diagnostics, Mutation Research, Blood, Clinical Cancer Research, Nature Medicine, Human Molecular Genetics, Journal of Thoracic Oncology

HONORS AND PRIZES

1991	<i>Magna cum Laude</i>	Yale University
1991	Academic Honors in Molecular Biochemistry and Biophysics	Yale University
1991	Academic Honors in Italian Studies	Yale University
1991-2000	Medical Scientist Training Program (MSTP)	SUNY at Stony Brook
2006	MGH Team Awards: Genetics in Medicine Implementation Team	Massachusetts General Hospital

2006	MGH Partners in Excellence Award	Massachusetts General Hospital
2007	MGH Partners in Excellence Award	Massachusetts General Hospital
2008	MGH Cancer Center "The One Hundred" awardee	Massachusetts General Hospital
2010	Dr. James Watson Healthcare Grant; Awarded Ion Torrent Next Generation Sequencer	Ion Torrent Corporation

PUBLICATIONS

>80 publications in the peer reviewed Journals.

NARRATIVE REPORT ON CAREER AND RESEARCH INTERESTS

1. Research

My major research interests include two areas of investigation: (1) large-scale copy number variation in the human genome and (2) molecular genetics of human neoplasia.

As a postdoctoral research fellow in the laboratory of Dr. Charles Lee at BWH, we used microarray-based comparative genomic hybridization (array CGH) to study normal human populations. We found unexpected large variations in genome segment copy number between individuals, termed large-scale copy number variants or CNVs. Subsequent studies have confirmed our findings, and have shown that CNVs are extremely common and can involve very large, contiguous regions of our genome. Current projections now suggest that any two individuals may have genomes that differ between 10-20 million bases of DNA sequence as a result of CNVs, far exceeding the total amount of DNA differences that are accounted for SNPs. Our research effort continues to explore the detailed genomic structure of these CNVs, and to assess their role in disease association. In addition we are developing probes corresponding to CNVs for *in situ* genetic analysis of identity.

My major research focus since joining the pathology department at MGH has been on applying molecular genetic techniques to the diagnosis and treatment of human neoplasia. One line of investigation has focused on diagnostics and clinico-pathologic evaluation of non-small cell lung cancer, including the description of morphologic correlates of EGFR and KRAS mutation and ALK-rearranged tumors in a large cohort of patients. We have screened large numbers of patients for entry into clinical trials of targeted agents. We found that ALK-positive lung tumors show a remarkable response to an ALK tyrosine kinase inhibitor.

We have also examined genetic alterations in tumors besides lung cancer, including FISH analysis of several hundred esophageal and stomach cancers for amplification of the *MET* gene, a recently-recognized genetic event that determines *in vitro* response to *MET* small molecular inhibitors. We have identified a subset of patients who would be eligible for a phase 1 clinical trial. As an extension of this study we have found approximately 10% of esophageal and stomach cancers also harbor *HER2* and *EGFR* amplification, and such patients will be enrolled in appropriate targeted therapy clinical trials. We are expanding our ability to screen patients for genetic signatures that will predict drug responsiveness in real time.

2. Teaching and clinical contributions

My principal teaching contributions involve direct supervision of 2-3 molecular genetic pathology fellows' 3 month clinical rotations, and organization and direct supervision of a 3 week molecular pathology clinical rotation for all pathology residents at MGH. I also give a number of didactic teaching sessions on tumor genetics each year including 6 sessions for the MGH pathology residents ("Outs" conference) and 3 sessions for MGH geneticists and fellows.

As director of Molecular Diagnostics and the Translational Research Laboratory, I oversee a new clinical laboratory service to support tumor diagnostics. The principle responsibilities include: (1) oversight of laboratory budget, including Capital and Operating budgets, (2) personnel hiring and management, (3) test development and validation using multiple advanced molecular techniques, (4) quality control and laboratory standard compliance, and (5) clinical report writing and sign-out. The lab employs 2 full-time PhD level directors, 10 full-time technicians, 1 clinical fellow and 2 post-doctoral fellows, and is in the process of expansion.

Talk at IAAO2011

Session; Personalized medicine; Targeting ALK-fusion

Title; A large scale screening of ALK fusions

Publications on ALK-related studies and those published in 2011.

1. Shaw AT, Forcione DG, Digumarthy SR, **lafrate AJ**. "Case records of the Massachusetts General Hospital. Case 21-2011. A 31-year-old man with ALK-positive adenocarcinoma of the lung." *N Engl J Med*. 2011 Jul 14;365(2):158-67.
2. Chiang S, Fazlollahi L, Nguyen A, Betensky RA, Roberts DJ, **lafrate AJ**. "Diagnosis of hydatidiform moles by polymorphic deletion probe fluorescence in situ hybridization." *J Mol Diagn*. 2011 Jul;13(4):406-15. Epub 2011 Apr 29.
3. Farris AB, Taheri D, Kawai T, Fazlollahi L, Wong W, Tolkoﬀ-Rubin N, Spitzer TR, **lafrate AJ**, Preffer FI, Locascio SA, Sprangers B, Saldman S, Smith RN, Cosimi AB, Sykes M, Sachs DH, Colvin RB. "Acute renal endothelial injury during marrow recovery in a cohort of

- combined kidney and bone marrow allografts." *Am J Transplant*. 2011 Jul;11(7):1464-77. doi: 10.1111/j.1600-6143.2011.03572.x. Epub 2011 Jun 10.
4. Ou SH, Kwak EL, Siwak-Tapp C, Dy J, Bergethon K, Clark JW, Camidge DR, Solomon BJ, Maki RG, Bang YJ, Kim DW, Christensen J, Tan W, Wilner KD, Salgia R, **Iafrate AJ**. "Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification." *J Thorac Oncol*. 2011 May;6(5):942-6.
 5. Le LP, Nielsen GP, Rosenberg AE, Thomas D, Batten JM, Deshpande V, Schwab J, Duan Z, Xavier RJ, Hornicek FJ, **Iafrate AJ**. "Recurrent chromosomal copy number alterations in sporadic chordomas." *PLoS One*. 2011;6(5):e18846. Epub 2011 May 13.
 6. Demicco EG, Farris AB 3rd, Baba Y, Agbor-Etang B, Bergethon K, Mandal R, Daives D, Fukuoka J, Shimizu M, Dias-Santagata D, Ogino S, **Iafrate AJ**, Gaissert HA, Mino-Kenudson M. "The dichotomy in carcinogenesis of the distal esophagus and esophagogastric junction: intestinal-type vs cardiac-type mucosa-associated adenocarcinoma." *Mod Pathol*. 2011 May 13. [Epub ahead of print]
 7. Zhu AX, Abrams TA, Miksad R, Blaszkowsky LS, Meyerhardt JA, Zheng H, Muzikansky A, Clark JW, Kwak EL, Schrag D, Jors KR, Fuchs CS, **Iafrate AJ**, Borger DR, Ryan DP. "Phase 1/2 study of everolimus in advanced hepatocellular carcinoma." *Cancer*. 2011 Apr 27. doi: 10.1002/cncr.26165. [Epub ahead of print]
 8. Katayama R, Khan TM, Benes C, Lifshits E, Ebi H, Rivera VM, Shakespeare WC, **Iafrate AJ**, Engelman JA, Shaw AT. "Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK." *Proc Natl Acad Sci U S A*. 2011 May 3;108(18):7535-40. Epub 2011 Apr 18.
 9. Dias-Santagata D, Lam Q, Vernovsky K, Vena N, Lennerz JK, Borger DR, Batchelor TT, Ligon KL, **Iafrate AJ**, Ligon AH, Louis DN, Santagata S. "BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: diagnostic and therapeutic implications." *PLoS One*. 2011 Mar 29;6(3):e17948.
 10. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, Akhavanfard S, Heist RS, Temel J, Christensen JG, Wain JC, Lynch TJ, Vernovsky K, Mark EJ, Lanuti M, **Iafrate AJ**, Mino-Kenudson M, Engelman JA. "Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors." *Sci Transl Med*. 2011 Mar 23;3(75):75ra26.
 11. Dias-Santagata D, Lam Q, Bergethon K, Baker GM, **Iafrate AJ**, Rakheja D, Hoang MP. "A potential role for targeted therapy in a subset of metastasizing adnexal carcinomas." *Mod Pathol*. 2011 Jul;24(7):974-82. doi: 10.1038/modpathol.2011.48. Epub 2011 Mar 18.
 12. Growdon WB, Roussel BN, Scialabba VL, Foster R, Dias-Santagata D, **Iafrate AJ**, Ellisen LW, Tambouret RH, Rueda BR, Borger DR. "Tissue-specific signatures of activating PIK3CA and RAS mutations in carcinosarcomas of gynecologic origin." *Gynecol Oncol*. 2011 Apr;121(1):212-7. Epub 2010 Dec 17.
 13. Farris AB 3rd, Demicco EG, Le LP, Finberg KE, Miller J, Mandal R, Fukuoka J, Cohen C, Gaissert HA, Zukerberg LR, Lauwers GY, **Iafrate AJ**, Mino-Kenudson M. "Clinicopathologic and molecular profiles of microsatellite unstable Barrett Esophagus-associated adenocarcinoma." *Am J Surg Pathol*. 2011 May;35(5):647-55.
 14. Camelo-Piragua S, Jansen M, Ganguly A, Kim JC, Cosper AK, Dias-Santagata D, Nutt CL, **Iafrate AJ**, Louis DN. "A sensitive and specific diagnostic panel to distinguish diffuse astrocytoma from astrocytosis: chromosome 7 gain with mutant isocitrate dehydrogenase 1 and p53." *J Neuropathol Exp Neurol*. 2011 Feb;70(2):110-5.
 15. Ting DT, Lipson D, Paul S, Brannigan BW, Akhavanfard S, Coffman EJ, Contino G, Deshpande V, **Iafrate AJ**, Letovsky S, Rivera MN, Bardeesy N, Maheswaran S, Haber DA. "Aberrant overexpression of satellite repeats in pancreatic and other epithelial cancers." *Science*. 2011 Feb 4;331(6017):593-6. Epub 2011 Jan 13.
 16. Corcoran RB, Dias-Santagata D, Bergethon K, **Iafrate AJ**, Settleman J, Engelman JA. "BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation." *Sci Signal*. 2010 Nov 23;3(149):ra84.
 17. Ou SH, Bazhenova L, Camidge DR, Solomon BJ, Herman J, Kain T, Bang YJ, Kwak EL, Shaw AT, Salgia R, Maki RG, Clark JW, Wilner KD, **Iafrate AJ**. "Rapid and dramatic radiographic and clinical response to an ALK inhibitor (crizotinib, PF02341066) in an ALK translocation-positive patient with non-small cell lung cancer." *J Thorac Oncol*. 2010 Dec;5(12):2044-6.
 18. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, Ou SH, Dezube BJ, Jänne PA, Costa DB, Varella-Garcia M, Kim WH, Lynch TJ, Fidias P, Stubbs H, Engelman JA, Sequist LV, Tan W, Gandhi L, Mino-Kenudson M, Wei GC, Shreeve SM, Ratain MJ, Settleman J, Christensen JG, Haber DA, Wilner K, Salgia R, Shapiro GI, Clark JW, **Iafrate AJ**. "Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer." *N Engl J Med*. 2010 Oct 28;363(18):1693-703.
 19. Dias-Santagata D, Akhavanfard S, David SS, Vernovsky K, Kuhlmann G, Boisvert SL, Stubbs H, McDermott U, Settleman J, Kwak EL, Clark JW, Isakoff SJ, Sequist LV, Engelman JA, Lynch TJ, Haber DA, Louis DN, Ellisen LW, Borger DR, **Iafrate AJ**. "Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine." *EMBO Mol Med*. 2010 May;2(5):146-58.
 20. Mino-Kenudson M, Chirieac LR, Law K, Hornick JL, Lindeman N, Mark EJ, Cohen DW, Johnson BE, Jänne PA, **Iafrate AJ**, Rodig SJ. "A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry." *Clin Cancer Res*. 2010 Mar 1;16(5):1561-71. Epub 2010 Feb 23.
 21. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, Solomon B, Stubbs H, Admane S, McDermott U, Settleman J, Kobayashi S, Mark EJ, Rodig SJ, Chirieac LR, Kwak EL, Lynch TJ, **Iafrate AJ**. "Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK." *J Clin Oncol*. 2009 Sep 10;27(26):4247-53. Epub 2009 Aug 10.
 22. Pao W, Kris MG, **Iafrate AJ**, Ladanyi M, Jänne PA, Wistuba II, Miake-Lye R, Herbst RS, Carbone DP, Johnson BE, Lynch TJ. "Integration of molecular profiling into the lung cancer clinic." *Clin Cancer Res*. 2009 Sep 1;15(17):5317-22. Epub 2009 Aug 25.
 23. Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY, Shaw A, Barletta JA, Stubbs H, Law K, Lindeman N, Mark E, Jänne PA, Lynch TJ, Johnson BE, **Iafrate AJ**, Chirieac LR. "Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population." *Clin Cancer Res*. 2009 Aug 15;15(16):5216-23. Epub 2009 Aug 11.
 24. McDermott U, **Iafrate AJ**, Gray NS, Shioda T, Classon M, Maheswaran S, Zhou W, Choi HG, Smith SL, Dowell L, Ulkus LE, Kuhlmann G, Greninger P, Christensen JG, Haber DA, Settleman J. "Genomic alterations of anaplastic lymphoma kinase may sensitize tumors to anaplastic lymphoma kinase inhibitors." *Cancer Res*. 2008 May 1;68(9):3389-95.
 25. McDermott U, Sharma SV, Dowell L, Greninger P, Montagut C, Lamb J, Archibald H, Raudales R, Tam A, Lee D, Rothenberg SM, Supko JG, Sordella R, Ulkus LE, **Iafrate AJ**, Maheswaran S, Njauw CN, Tsao H, Drew L, Hanke JH, Ma XJ, Erlander MG, Gray NS, Haber DA, Settleman J. "Identification of genotype-correlated sensitivity to selective kinase inhibitors by using high-throughput tumor cell line profiling." *Proc Natl Acad Sci U S A*. 2007 Dec 11;104(50):19936-41. Epub 2007 Dec 6.