2007 Curt Stern Award ~ Introduction of Jeffrey Murray by Anne Bowcock

It is my pleasure to introduce the 2007 Curt Stern awardee, Jeffrey Murray. The Curt Stern Award was established in 2001 and recognizes scientific excellence in the field of human genetics on the basis of research performed over the last 10 years. In particular, this award is given to a recipient not only as a mark of outstanding scientific achievement, but also to a researcher who has pioneered an area of research that has significantly advanced the field of human genetics.

Jeff Murray is an exemplary example of such a recipient who has also had a major impact on clinical care. Jeff completed his BS degree at MIT and his MD at Tufts University school of medicine. After pediatric residency and fellowship training in New England and in Seattle he joined the faculty at the University of Iowa College of Medicine in 1984 where he is currently Professor of Pediatrics and where he holds the Roy J Carver Chair in Perinatal Health. Jeff has contributed widely to many areas of human genetics and genomics. For example, his work in large-scale genetic mapping was one of the early successes of the human genome project. However, Jeff's major area of research over the past twenty years has been in the genetics of orofacial clefting. Cleft lip and palate are frequent birth defects worldwide and represent a common complex disease. Jeff has pioneered the search for the genetic and environmental causes of this spectrum of disorders. Over the past ten years his work has resulted in an explosion in our knowledge of the molecular genetics of clefting. Jeff has put together a remarkable network of clinicians, scientists and patient groups. This multidisciplinary alliance has directly resulted in the identification of a series of genes that play significant roles in orofacial clefting, and in the discovery of variants that affect gene environment interactions. His group has published over a hundred papers on various aspects of orofacial clefting in the last ten years alone.

In addition to his accomplishments as a research scientist, Jeff is an active clinician who has given a great deal back to the patient population and particularly to underserved patient populations throughout the world. Over the years he has trained dozens of clinicians and scientists from many different countries as well as those in his laboratory.

Jeff has had a global influence upon the entire field of orofacial clefting, both in his pioneering work on the molecular genetic underpinnings of these birth defects and in the clinical care of affected patients. He is currently conducting clinical trials of folic acid dietary supplementation and its effects on cleft recurrence prevention in various areas of the world.

There were many highly qualified nominees for this years Curt Stern Award award but Jeff was the clear and unanimous choice of the awards committee.

On behalf of the American Society of Human Genetics and as a member of the Awards Committee, I am privileged to present the 2007 Curt Stern Award to Dr. Jeffrey Murray.

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2007 CURT STERN AWARD PRESENTATION
BY
JEFFREY C. MURRAY, MD
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TITLE: A CAREER INVESTIGATING CLEFT LIP AND PALATE

First, I would like to thank the nominators and the Society for the opportunity for me to be awarded the Curt Stern Award. This is a tremendous honor to me personally and far more importantly to the many collaborators and students I have worked with over the years on investigations into the etiology and outcomes of children born with cleft lip and palate. It is a particular honor in that Curt Stern had a long-standing interest in the interface between genetics, medicine and ethics from his earliest years of training with Thomas H. Morgan in Drosophila Genetics at Columbia. Curt Stern's career spanned the genetics of the 20th Century including not only his work with Morgan but also close contact with Herman Muller and the identification of radiation as a source of direct genetic change[1]. He was an active discussant on the issues of genetics, intelligence and race[2]. This interface of science and politics is one that is on-going today and it is important for students to recognize that their scientific interests can have important social implications. The discussions by Stern and his respondents[3] are entirely reminiscent of the dialogue ongoing 57 years later about race and intelligence.

Our own work benefited greatly in beginning in the area of cleft lip and palate from the insights of a wide-range of highly experienced clinicians who trained me directly such as Bonnie Pagon, Hans Zellweger, Jim Hanson and especially Murray Feingold who first exposed me to quality care for patients with birth defects. Other clinicians such as Mike Cohen, Bob Gorlin, Antonio Richieri Costa and Marilyn Jones have provided wonderful insights into the spectrum of cleft lip and palate and its associated anomalies that has been essential for the molecular work to proceed. Coupled to the work of the dedicated surgeons I have had the opportunity to work alongside of such as John Canady, Steve Gray, and Janusz Bardach I have had the opportunity to think deeply about the clinical spectrum and the surgical response and I believe that this has helped to better inform the work that we do both motivationally and scientifically.

Our work began with a postdoctoral fellow, Holly Ardinger, in the application of genetic technologies that I had learned under the mentorship of Arno Motulsky, George Stamatoyannopoulus and Clem Furlong at the University of Washington[4]. As a new assistant professor, I was eager to apply the techniques of RFLPs and Southern blots to questions of human genetics. Cleft lip and palate initially seemed an ideal model for

this in that it was both a common complex trait with important clinical implications but also had single gene models such as Van der Woude syndrome that would be more tractable to the linkage and gene finding approaches of the 1980s and 1990s as presaged eloquently by Dr. Fraser[5]. I was very fortunate to have John Philips at Vanderbilt refer me to Operation Smile and the volunteer medical missions that Bill and Kathy Magee and their teams did on children with cleft lip and palate around the world and in particular in the Philippines. We were able to establish a program in the Philippines that is ongoing today in identifying families with multiple affected members with clefts. We provide them with support through our nursing field workers for the management of these children and also work with them on research protocols to develop an understanding of the genetic and environmental causes of these birth defects[6]. Sandy Daack-Hirsch in Iowa and Edith Villanueva in the Philippines have been the leaders of this work for over 15 years.

This early work in the Philippines was done jointly with Ken Buetow. Ken, Kate Mills and Graeme Bell were my first close scientific collaborators and made me realize how important and useful working with nice, smart people can be. Ken had done terrific work on linkage disequilibrium with Aravinda Chakravarti[7] and we began to investigate its use in gene mapping while he was a graduate student and I was a postdoctoral fellow. We had a seminal experience at the Human Gene Mapping meeting in Helsinki in 1985. In an amazing week of seeing the giants in the field of genetics take the time to talk to us two neophytes we developed the idea of using linkage disequilibrium as a form of gene mapping and of identifying functional variants in the absence of knowledge of biology. This work was published as a speculation as part of an article in the American Journal of Human Genetics[8] and remains one of my most exciting moments in science. We have been happy to see this concept now come to dominate this years ASHG meetings in the form of genome wide association studies.[9]

In the mid-1990s I was able to establish an extremely fruitful collaboration with Kaare Christensen in Denmark who had trained under Paul Fogh-Andersen whose thesis in 1942 very carefully elucidated the genetic distinctions between cleft lip and palate in distinction to cleft palate only and also the familial nature of the disorder[10]. Kaare, together with Laura Mitchell and others, has been able to make use of the terrific resources available through the Danish National Health Care System and National Registries for clefts, twins, and other phenotypic traits to study genes, epidemiology, and outcomes[11]. Kaare and his colleagues work has been highly successful in demonstrating that you can determine explicit recurrence traits for clefting within families and perhaps more importantly that the long-term outcomes of children born with clefts are not limited to the surgical and speech challenges that are so readily recognized but also have long term implications such as breast cancer[12] and increased life long mortality[13]. This has now enabled us to expand our interest in these epidemiologic and genetic findings into looking at the genetic variables that may influence long term outcomes as well.

While the epidemiologic studies were going on internationally, a group of close collaborators, Mary Marazita, Andrew Lidral, Brian Schutte, and Mike Dixon have also

continued to investigate the molecular events contributing to cleft lip and palate. We were very fortunate, following a suggestion by Rich Pauli, to build on the work of Bocian and Walker[14] to demonstrate that the *IRF6* gene is responsible for mutations in the autosomal dominant form of clefting associated with lip pits, the Van der Woude syndrome[15]. This work built on the efforts of a series of dedicated students (Darryl Nishimura, Brian Bjork, Achim Sander, Yoko Watanabe and Shinji Kondo). Brian Schutte and Mike Dixon have now developed a highly productive mouse model for the *IRF6* gene in demonstrating the critical role that it plays in skin development and potentially wound healing[16,17]. In complementary efforts, Theresa Zucchero was able to demonstrate that a haplotype associated with the *IRF6* gene was associated with the common, isolated or nonsyndromic form of cleft lip and palate as well[18]. This resulted from the forging of an international collaboration with more than 8000 samples collected from Europe, North America, South America and Asia to demonstrate a highly significant statistical finding. Most recently, and presented at this meeting, Fedik Rahimov in our lab, has gone on to identify what we believe is the specific point mutation contained within the haplotype block that is responsible for about a 15% attributable risk for clefting in humans in a very beautiful study that coupled multi-sequenced conserved element analysis with a variety of biological and functional assays. That work benefited from the technology development of the Human Genome Project and in particular Eric Green's efforts at the NISC to provide publicly available information on multi-species DNA sequence comparisons to identify regulatory elements and in our case a critical enhancer element located about 10 kb upstream of the *IRF6* gene.

Other candidate gene efforts in our lab and others have also been successful, including identification of a role for point mutations in the*TGFB3* gene[19] *MSX1* gene[20,21], the *FGFR* gene pathway[22], *PVR*[23], *PVRL1*[24], *PTCH*[25] as well as modest contributions from other genes as well, such as *FOXE1*[26]. The labs of Koh-ichiro Yoshiura for *RYK*[27], Jacqui Hecht for *CRISPLD2*[28] and *MYH9*[29] have also identified rare point mutations or strong associations that appear to be etiologic in a small proportion of isolated cleft cases.

We also felt that it was critical to assess the role of the environment in these etiologic studies as well[30]. Recently a strong correlation between a fetal genotype for *GSTT1* and maternal smoking has been demonstrated[31,32]. In fact, it is a great honor for me that on this very stage that I am currently receiving the Curt Stern Award, Min Shi just received the Cotterman Award for her work on *GSTT1*. Investigations into environmental etiologies have also been carried out by Paul Romitti[33], Ron Munger[34], Ed Lammer with Gary Shaw and Rick Finnell[35,36], and others[37,38,39,40] to provide a more comprehensive picture of the contributions of vitamins, diet, folic acid, alcohol, smoking and other variables.

Lastly, our early work in cleft lip and palate provided us with the opportunity to see the tremendous impact this had on individuals and families that extended beyond the surgical and dental requirements to psychology, speech, and other developmental issues. This provided us with a stimulus to also determine whether we could begin

clinical trials work to either lower the burden of cleft lip and palate recurrence within families or to provide efforts to improve outcomes of children born with these defects[41]. We focused particularly on less developed countries where the burdens were potentially higher as access to medical care was more limited. In a series of studies in collaboration with Ed Castilla and the ECLAMC group in South America and Danilo Moretti-Ferreira and Jose Alberto de Souza Freitas in Brazil we have now had the opportunity to begin this work. Two outcome clinical trials are underway throughout South America using the ECLAMC collaboration, one looking at whether early pediatric care interventions can decrease mortality in children born with clefts at one month of age and a second looking at whether their morbidities at two years, as well as growth and development, can be affected by more aggressive and focused early care. All of this field work has been supervised by George Wehby and Norman Goco. We have been fortunate to acquire funding initially from the NICHD and Gates Foundation and now from the NIDCR to carry out a very large clinical trial in Brazil to investigate the possibility that high dose folic acid supplementation in women of childbearing age with a family history of clefting may result in lowered recurrence risks. Although the results will not be available for several more years, we are enthusiastic about the specific opportunities presented here and also for the recognition that children born with birth defects might be intensively investigated using clinical trial activities and by the application of health economics to understanding impact and outcomes [42,43].

These efforts in cleft lip and palate have had some preliminary successes, and we now believe that we are beginning to come to a point where we can provide parents with more specific information about the recurrence risks and the likely outcome of their children born with clefts. Whole new arenas of investigation are now opening into behavioral[44], brain structure correlates[45], and other subphenotypes[46]. In addition the application of genomic technologies as well as more elegant use of existing populations such as monozygotic twins[47,48] afford options to efficiently identify gene/environment and epigenetic roles in clefting.

In parallel with this work has been the recognition that in less developed countries a wide range of infectious and poverty related diseases, many preventable through immunizations, still plague the vast majority of children and families on our planet. I have had the opportunity to work in hospitals where children continue to die from measles and tetanus and the impact of such a death on a family is no less than it would be in any family suffering the loss of a child. For us as health care professionals, the impact is perhaps substantially increased by the recognition that these are readily preventable disorders through routine immunizations available throughout the developed world. We should give significant thanks to organizations such as the Gates Foundation which are now using their financial resources to specifically target diseases affecting underprivileged women and children around the globe. It is my own hope that the work we carry out on the genetics of a birth defect can stimulate students coming into the field to recognize the importance and excitement of investigating a particular disorder, but to also retain a larger sense of the problems of health care facing the world as a whole. One should always set aside a portion of their time to not only investigate the conditions that they are most motivated to work on directly but to also work towards

implementing social justice across all populations. As an organization, the American Society of Human Genetics has often played a leadership role in aspects of social justice related to genetics and we are particularly fortunate this year to have Dr. Burke as our president who has had a long standing commitment to the ethical, legal, and social implications of the work that we do[49].

While it is an honor to receive the Curt Stern Award and I am grateful to the many collaborators and students whose award this truly is, I hope that in future years the Curt Stern Award will also be able to reflect a success in our movement into addressing some of the broader issues of genetics and justice as well. Again I thank the Society, my nominators, and my many colleagues and students who have made this work enjoyable, fun, we hope somewhat productive, and to apologize to the many colleagues and collaborators whose work I was unable to include.

Acknowledgments

Besides the many students and colleagues noted above I would also like to thank my terrific laboratory and administrative staff. The many patients and families who have worked with us and the volunteers of Operation Smile, the HOPE Foundation has been critical to this work. I have also greatly benefited from strong Division Heads (Jim Hanson, Ed Bell and Jeff Segar) and Department Chairs (Fred Smith, Frank Morriss and Mike Artman) who have given me space and time to find my way and from terrific support from the NIDCR over many years and in particular our program officers Judy Small and Rochelle Small and the Directors Hal Slavkin and Larry Tabak. Finally, I would like to dedicate this work to Achim Sander, Steve Gray and John Wasmuth – three colleagues who worked hard to bring the best to families but who died far too early.

References

1. Uphoff DE, Stern C (1949) The genetic effects of low intensity irradiation. Science Jun 17;109(2842):609-610
2. Stern C (1949) Selection and eugenics. Science Aug 26;110(2852):201-208
3. Stern B (1950) Does genetic endowment vary by socioeconomic group. Science 111:697-699
4. Ardinger HH, Buetow KH, Bell GI, Bardach J, VanDemark DR, Murray JC (1989) Association of genetic variation of the transforming growth factor-alpha gene with cleft lip and palate. Am J Hum Genet Sep;45(3):348-353
5. Fraser FC. (1970) The genetics of cleft lip and cleft palate. Am J Hum Genet May;22(3):336-352
6. Murray JC, Daack-Hirsch S, Buetow KH, Munger R, Espina L, Paglinawan N, Villanueva E, Rary J, Magee K, Magee W (1997) Clinical and epidemiologic studies of cleft lip and palate in the Philippines. Cleft Palate Craniofac J Jan;34(1):7-10
7. Chakravarti A, Buetow KH, Antonarakis SE, Waber PG, Boehm CD, Kazazian HH (1984) Nonuniform recombination within the human beta-globin gene cluster Am J Hum Genet Nov;36(6):1239-58

8. Murray JC, Buetow KH, Donovan M, Hornung S, Motulsky AG, Disteche C, Dyer K, Swisshelm K, Anderson J, Giblett E, et al (1987) Linkage disequilibrium of plasminogen polymorphisms and assignment of the gene to human chromosome 6q26-6q27. Am J Hum Genet Apr;40(4):338-50
9. Christensen K, Murray JC (2007) What genome-wide association studies can do for medicine. N Engl J Med Mar 15;356(11):1094-7
10. Fogh-Andersen P (1942) Inheritance of harelip and cleft palate. Copenhagen: Munksgaard
11. Christensen K, Mitchell LE (1996) Familial recurrence-pattern analysis of nonsyndromic isolated cleft palate--a Danish Registry study. Am J Hum Genet Jan;58(1):182-190
12. Bille C, Falck Winther J, Bautz A, Murray JC, Olsen J, Christensen K (2005) Cancer Risk in Persons with Oral Cleft – A Population-based Study of 8,093 cases. Am J Epidemiol 161(11):1047-1055
13. Christensen K, Juel K, Herskind AM, Murray JC (2004) Long term follow up study of survival associated with cleft lip and palate at birth. Br Med J 328(7453):1405-1409
14. Bocian M, Walker AP (1987) Lip pits and deletion 1q32----41. Am J Med Genet Feb;26(2):437-443
15. Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, Howard E, Ferreira de Lima RLL, Daack-Hirsch S, Sander A, McDonald-McGinn DM, Zackai EH, Lammer EJ, Aylsworth AS, Ardinger HH, Lidral AC, Pober BR, Moreno L, Arcos-Burgos M, Valencia C, Houdayer C, Bahuau M, Moretti-Ferreira D, Richieri-Costa A, Dixon MJ, Murray JC (2002) Mutations in *IRF6* cause Van der Woude and popliteal pterygium syndromes. Nat Genet 32(2):285-289
16. Richardson RJ, Dixon J, Malhotra S, Hardman MJ, Knowles L, Boot-Handford RP, Shore P, Whitmarsh A, Dixon MJ (2006) Irf6 is a key determinant of the keratinocyte proliferation-differentiation switch. Nat Genet Nov;38(11):1329-1334
17. Ingraham CR, Kinoshita A, Kondo S, Yang B, Sajan S, Trout KJ, Malik MI, Dunnwald M, Goudy SL, Lovett M, Murray JC, Schutte BC (2006) Abnormal skin, limb and craniofacial morphogenesis in mice deficient for interferon regulatory factor 6 (Irf6). Nat Genet Nov;38(11):1335-1340
18. Zucchero TM, Cooper ME, Maher BS, Daack-Hirsch S, Nepomuceno B, Ribeiro L, Caprau D, Christensen K, Suzuki Y, Machida J, Natsume N, Yoshiura K, Vieira AR, Orioli IM, Castilla E, Moreno L, Arcos-Burgos M, Lidral AC, Field LL, Liu Y, Ray A, Goldstein TH, Schultz R, Shi M, Johnson M, Kondo S, Schutte B, Marazita ML, Murray JC (2004) Interferon regulatory factor 6 (IRF6) is a modifier for isolated cleft lip and palate. N Engl J Med 351(8):769-780
19. Lidral AC, Romitti PA, Basart AM, Doetschman T, Leysens NJ, Daack-Hirsch S, Semina EV, Johnson LR, Machida J, Burds A, Parnell TJ, Rubenstein JL, Murray JC (1998) Association of MSX1 and TGFB3 with nonsyndromic clefting in humans. Am J Hum Genet Aug;63(2):557-568
20. Jezewski PA, Vieira AR, Nishimura C, Ludwig B, Johnson M, O'Brien SE, Daack-Hirsch S, Schultz RE, Weber A, Nepomucena B, Romitti PA, Christensen K, Orioli IM, Castilla EE, Machida J, Natsume N, Murray JC (2003) Complete sequencing shows a role for *MSX*1 in non-syndromic cleft lip and palate. J Med Genet 40:399-407

21. Suzuki Y, Jezewski PA, Machida J, Watanabe Y, Shi M, Cooper ME, Viet LT, Tin NTD, Hai H, Natsume N, Shimozato K, Marazita ML, Murray JC (2004) In a Vietnamese population, *MSX1* variants contribute to cleft lip and palate. Genet Med 6(3):117-125
22. Riley BM, Mansilla MA., Ma J, Daack-Hirsch S, Maher BS, Raffensperger LM, Russo ET, Vieira AR, Dode C., Mohammadi M, Marazita ML, Murray JC (2007) Impaired FGF signaling contributes to cleft lip and palate. Proc Natl Acad Sci U S A Mar 13;104(11):4512-4517, Epub 2007 Mar 6
23. Warrington A, Vieira AR, Christensen K, Orioli IM, Castilla EE, Romitti PA, Murray JC (2006) Genetic evidence for the role of loci at 19q13 in cleft lip and palate J Med Genet 43(6):e26
24. Avila JR, Jezewski PA, Vieira AR, Orioli IM, Castilla EE, Christensen K, Daack-Hirsch S, Romitti PA, Murray JC (2006) PVRL1 variants contribute to nonsyndromic cleft lip and palate in multiple populations. Am J Med Genet A. Dec 1;140(23):2562-2570
25. Mansilla MA, Cooper ME, Goldstein T, Castilla EE, Lopez Camelo JS, Marazita ML, Murray JC. (2006) Contributions of PTCH gene variants to isolated cleft lip and palate. Cleft Palate-Craniofac J 43(1):21-29
26. Vieira AR, Avila JR, Daack-Hirsch S, Dragan E, Félix TM, Rahimov F, Harrington J, Schultz RR, Watanabe Y, Johnson M, Fang J, O'Brien ES, Orioli IM, Castilla EE, FitzPatrick DR, Jiang R, Marazita M, Murray J (2005) Medical sequencing of candidate genes for nonsyndromic cleft lip and palate. PLoS Genet Dec 1(6):e64
27. Watanabe A, Akita S, Tin NT, Natsume N, Nakano Y, Niikawa N, Uchiyama T, Yoshiura K (2006) A mutation in RYK is a genetic factor for nonsyndromic cleft lip and palate. Cleft Palate Craniofac J May;43(3):310-316
28. Chiquet BT, Lidral AC, Stal S, Mulliken JB, Moreno LM, Arco-Burgos M, Valencia-Ramirez C, Blanton SH, Hecht JT (2007) CRISPLD2: a novel NSCLP candidate gene. Hum Mol Genet Sep 15;16(18):2241-2248
29. Martinelli M, Di Stazio M, Scapoli L, Marchesini J, Di Bari F, Pezzetti F, Carinci F, Palmieri A, Carinci P, Savoia A (2007) Cleft lip with or without cleft palate: implication of the heavy chain of non-muscle myosin IIA. J Med Genet Jun;44(6):387-392
30. Mossey P (2007) Epidemiology underpinning research in the aetiology of orofacial clefts. Orthod Craniofac Res Aug;10(3):114-120
31. Lammer EJ, Shaw GM, Iovannisci DM, Finnell RH. (2005) Maternal smoking, genetic variation of glutathione s-transferases, and risk for orofacial clefts. Epidemiology Sep;16(5):698-701
32. Shi M, Christensen K, Weinberg CR, Romitti P, Bathum L, Lozada A, Morris RW, Lovett M, Murray JC (2007) Orofacial cleft risk is increased with maternal smoking and specific detoxification gene variants. Am J Hum Genet 80(1):76-90
33. Romitti PA, Sun L, Honein MA, Reefhuis J, Correa A, Rasmussen SA. (2007) Maternal periconceptional alcohol consumption and risk of orofacial clefts. Am J Epidemiol Oct 1;166(7):775-85
34. Munger RG, Romitti PA, Daack-Hirsch S, Burns TL, Murray JC, Hanson J (1996) Maternal alcohol use and risk of orofacial cleft birth defects. Teratology Jul;54(1):27-33
35. Lammer EJ, Shaw GM, Iovannisci DM, Van Waes J, Finnell RH (2004) Maternal

smoking and the risk of orofacial clefts: Susceptibility with NAT1 and NAT2 polymorphisms. Epidemiology Mar;15(2):150-156
36. Shaw GM, Nelson V, Iovannisci DM, Finnell RH, Lammer EJ (2003) Maternal occupational chemical exposures and biotransformation genotypes as risk factors for selected congenital anomalies. Am J Epidemiol Mar 15;157(6):475-484
37. Werler MM, Hayes C, Louik C, Shapiro S, Mitchell AA. (1999) Multivitamin supplementation and risk of birth defects. Am J Epidemiol Oct 1;150(7):675-682
38. Badovinac RL, Werler MM, Williams PL, Kelsey KT, Hayes C (2007) Folic acid-containing supplement consumption during pregnancy and risk for oral clefts: a meta-analysis. Birth Defects Res A Clin Mol Teratol Jan;79(1):8-15
39. Vujkovic M, Ocke MC, van der Spek PJ, Yazdanpanah N, Steegers EA, Steegers-Theunissen RP (2007) Maternal Western dietary patterns and the risk of developing a cleft lip with or without a cleft palate. Obstet Gynecol Aug;110(2 Pt 1):378-384
40. Zeiger JS, Beaty TH, Liang KY (2005) Oral clefts, maternal smoking, and TGFA: a meta-analysis of gene-environment interaction. Cleft Palate Craniofac J Jan;42(1):58-63
41. Wehby GL, Castilla EE, Goco N, Rittler M, Cosentino V, Javois L, McCarthy AM, Bobashev G, Litavecz S, Mariona A, Dutra G, López-Camelo JS, Orioli IM, Murray JC (2006a) Description of the methodology used in an ongoing pediatric care interventional study of children born with cleft lip and palate in South America [NCT00097149]. BMC Pediatr Mar 24;6:9
42. Wehby GL, Ohsfeldt RL, Murray JC (2006b) Health professionals' assessment of health-related quality of life values for oral clefting by age using a visual analogue scale method. Cleft Palate Craniofac J Jul;43(4):383-391
43. Damiano PC, Tyler MC, Romitti PA, Momany ET, Jones MP, Canady JW, Karnell MP, Murray JC (2007) Health-related quality of life among preadolescent children with oral clefts: the mother's perspective. Pediatrics Aug;120(2):e283-290
44. Richman LC, Ryan SM (2003) Do the reading disabilities of children with cleft fit into current models of developmental dyslexia? Cleft Palate Craniofac J Mar;40(2):154-157
45. Nopoulos P, Langbehn DR, Canady J, Magnotta V, Richman L (2007) Abnormal brain structure in children with isolated clefts of the lip or palate. Arch Pediatr Adolesc Med Aug;161(8):753-758
46. Marazita ML (2007) Subclinical features in non-syndromic cleft lip with or without cleft palate (CL/P): review of the evidence that subepithelial orbicularis oris muscle defects are part of an expanded phenotype for CL/P. Orthod Craniofac Res May;10(2):82-87
47. Mansilla MA, Kimani J, Mitchell LE, Christensen K, Boomsma DI, Daack-Hirsch S, Nepomucena B, Wyszynski DF, Felix TM, Martin NG, Murray JC (2005) Discordant MZ twins with cleft lip and palate: a model for identifying genes in complex traits. Twin Res Hum Genet Feb;8(1):39-46
48. Kimani JW, Shi M, Daack-Hirsch S, Christensen K, Moretti-Ferreira D, Marazita ML, Field LL, Canady JW, Murray JC (2007) X-chromosome inactivation patterns in monozygotic twins and sib pairs discordant for nonsyndromic cleft lip and/or palate. Am J Med Genet A Nov 14;143A(24):3267-3272
49. Dudzinski DM, Burke W (2006) Practicing moral medicine: patient care to public

health. Am J Bioeth Mar-Apr;6(2):75-6