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The crossroads of health care research and health care delivery*

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Citation: Backeljauw, Philippe F. et al. "Proceedings from the Turner Resource Network Symposium: The Crossroads of Health Care Research and Health Care Delivery." *American Journal of Medical Genetics Part A* 167.9 (2015): 1962–1971.

As Published: <http://dx.doi.org/10.1002/ajmg.a.37121>

Publisher: Wiley Blackwell

Persistent URL: <http://hdl.handle.net/1721.1/109921>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

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Published in final edited form as:

Am J Med Genet A. 2015 September ; 0(9): 1962–1971. doi:10.1002/ajmg.a.37121.

Proceedings From the Turner Resource Network Symposium: The Crossroads of Health Care Research and Health Care Delivery

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Abstract

Turner syndrome, a congenital condition that affects ~1/2,500 births, results from absence or structural alteration of the second sex chromosome. There has been substantial effort by numerous clinical and genetic research groups to delineate the clinical, pathophysiological, cytogenetic, and molecular features of this multisystem condition. Questions about the molecular-genetic and biological basis of many of the clinical features remain unanswered, and health care providers and

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families seek improved care for affected individuals. The inaugural “Turner Resource Network (TRN) Symposium” brought together individuals with Turner syndrome and their families, advocacy group leaders, clinicians, basic scientists, physician-scientists, trainees and other stakeholders with interest in the well-being of individuals and families living with the condition. The goal of this symposium was to establish a structure for a TRN that will be a patient-powered organization involving those living with Turner syndrome, their families, clinicians, and scientists. The TRN will identify basic and clinical questions that might be answered with registries, clinical trials, or through bench research to promote and advocate for best practices and improved care for individuals with Turner syndrome. The symposium concluded with the consensus that two rationales justify the creation of a TRN:

1. inadequate attention has been paid to the health and psychosocial issues facing girls and women who live with Turner syndrome;
2. investigations into the susceptibility to common disorders such as cardiovascular or autoimmune diseases caused by sex chromosome deficiencies will increase understanding of disease susceptibilities in the general population.

Keywords

monosomy X; Turner syndrome; women; congenital heart disease; genetics; neurodevelopment; chromosome; sex chromosomes; women's health; quality of life

Introduction

The First Turner Resource Network (TRN) Symposium was held July 13–14, 2014 in Jacksonville, Florida in conjunction with the 27th Annual Conference of the Turner Syndrome Society of the United States (TSSUS). The symposium brought together adults and children with Turner syndrome, their families, and representatives from other Turner syndrome support and advocacy groups, including the Turner Syndrome Foundation and the Turner Syndrome Global Alliance, clinicians and basic scientists, trainees and other stakeholders. A major theme of the gathering was to highlight the considerable accomplishment of the Turner syndrome community itself. Participants included women living with Turner syndrome from all walks of life including mothers, daughters, lawyers, judges, administrators, pediatricians, internists, endocrinologists, clinical geneticists, and psychologists among others. By virtue of the free exchange of ideas that occurred during the two-day event, these advocates challenged and engaged the entire group of more than 200 participants.

Prior to the meeting, a survey developed by the Advocacy Committee of the TRN was distributed to the members of the Turner Syndrome Society of the United States, and gathered responses from more than 700 individuals. The survey results were a focal point of the symposium and will direct the activities of the TRN going forward.

The symposium itself had three closely interrelated goals:

1. To identify the major health policy issues facing girls and women living with Turner syndrome (Session I, “Health Care Policy and Health Care Delivery for TS Patients”);
2. To review basic and clinical questions that might be answered by either bench research, clinical trials, clinical datasets or registries (Session II, “Turner Science: From Genotype to Phenotype”); and
3. To discuss a strategy for how a national network of regional Turner syndrome resource centers (the TRN) will be organized (“Session III: The TRN roadmap”).

Turner syndrome is a rare heterogeneous condition caused by absence of all or part of the second sex chromosome in at least a proportion of the body's cells in individuals with a female phenotype. How underlying mechanisms related to X monosomy at the level of individual tissues bring about the varied phenotypic features remains largely unknown. Importantly, the impact of the genetic deficiencies on numerous body systems creates interrelated challenges for those who live with Turner syndrome that society and the U.S. health care system in general have barely begun to address. These problems include ovarian insufficiency, infertility, and problems with the lymphatic system. In addition, there is an increased prevalence of numerous common conditions that affect the general public, including cardiovascular disease, hypertension, stroke, and autoimmune dysfunction. Many girls and women with Turner syndrome have to deal with chronic and recurrent otitis media, conductive and sensorineural hearing impairment, orthopedic and dental issues and some also must address neuropsychological problems that include learning disability, executive function dysregulation and specific areas of cognitive and social challenge. Compelling epidemiological evidence indicates a threefold higher death rate (primarily due to cardiovascular causes) in women with Turner syndrome compared to the risk for the general female population at the equivalent age (Fig. 1) [Schoemaker et al., 2008].

Two rationales have energized the stakeholders to make the TRN initiative a success:

1. Unacceptable levels of morbidity/mortality and the lack of access comprehensive health care among girls and women living with Turner syndrome must be addressed, and
2. Susceptibility to common conditions caused by deficiencies of X/Y-chromosomal genes will lead to an understanding of disease susceptibilities in the general population.

This novel second rationale was introduced during the first morning of the symposium by Dr. David C. Page, the Director of the Whitehead Institute and a Professor at the Massachusetts Institute of Technology. A summary of Dr. Page's comments provided here is followed by a summary of the meeting presentations (Section II), speakers' abstracts (Section III) and a TRN roadmap (Section IV, breakout sessions).

How Understanding Turner Syndrome Will Teach us About Health and Disease in the General Population. David C. Page, MD

The question of Turner syndrome's origin is far more complex than it may seem, and answering it will lead us to a broader understanding of the role of the sex chromosomes in

health and disease. Turner syndrome was equated with monosomy X in 1959, and to this day, it is still considered to be a chromosomal anomaly. However, when Henry Turner and Otto Ullrich first defined the disorder in the 1930s, they were not describing a chromosomal anomaly but a clinical phenotype. To fully understand the interplay between this chromosomal anomaly and the complex Turner phenotype, we need to disentangle several related questions. We could begin by asking: What causes monosomy X? When during sex cell or embryonic development does the loss of the second sex chromosome occur? We now know that most females with Turner syndrome have a chromosome anomaly in only a subset of their cells and tissues. Moreover, not everybody with Turner syndrome has monosomy X. The diagnosis actually refers to a grab bag of clinical anomalies in combination with the absence of all or part of a second sex chromosome, either the X or the Y. We are now in the position to ask a different question: How does the absence of all or part of a second sex chromosome result in the clinical features of the syndrome described by Henry Turner and Otto Ullrich?

Asking this question creates a connection between the study of Turner syndrome and broader research on how genetic and molecular differences between males and females lead to differences in health and disease. In 1993, my laboratory colleagues and I, hypothesized that the phenotypic features of Turner syndrome result from having just a single dose (rather than a double dose) of genes that are common to the X and Y chromosomes and that escape X inactivation [Watanabe et al., 1993; Zinn et al., 1993]. During most of the two decades since, and indeed until very recently, progress in this area had been slow; even today, studies of the sex chromosomes lag behind the rest of the genome. Most notably, researchers pursuing genetic understanding through genome wide association studies (GWAS) had mostly excluded the X and Y chromosomes from their investigations, largely for technical reasons.

I envision an opportunity for the sex chromosomes to return to a place of prominence in our understanding of health and disease. When you compare an XY male to an XX female, they are only 98.5 percent the same in their genomes: 15 times the genetic difference when comparing two males or two females. These differences may manifest themselves phenotypically. For example, the incidence of rheumatoid arthritis is 2–3 times greater in women than in men. Five boys are affected by autism spectrum disorder for every girl who is diagnosed. The ratio of females to males diagnosed with lupus is six to one. In the case of dilated cardiomyopathy, affected men tend to die about 10 years earlier than affected women. In none of these cases is the disease related to the reproductive tract, but should ultimately be accounted for by sex chromosomal differences between XY males and XX females.

To understand our sex chromosomes more deeply, we must turn to evolution. The human X and Y chromosomes evolved from an identical pair of autosomes. The X chromosome has retained nearly all of the 649 genes present on the ancestral autosomes, while the Y chromosome has retained only 17. The 17 survivors, shared by both the X and Y chromosomes today, turn out to be involved in regulating the activity of other genes throughout our entire genome [Bellott et al., 2014]. We have strong evidence that 12 of these genes are needed in two copies—one in each of the two sex chromosomes present in

XX or XY cells—to function properly. It is likely that Turner syndrome patients, lacking a second sex chromosome, manifest disease because of the haploinsufficiency of these 12 genes. We should be able to account for the genetic varieties of Turner syndrome by understanding these genes shared by the X and Y chromosomes. In addition, an understanding of the genetic basis of disease susceptibility caused by deficiencies of the second sex chromosome will help us to understand the panoply of differences between men and women in health and disease. In sum, I suggest that we forge strong links between research on Turner syndrome and research on sex differences in disease generally.

Short Summaries of Meeting Presentations (Abstracts from Each Presentation are Provided Below and an eBook Containing the Entire Proceedings is Planned for Publication Summer 2015)

Dr. Stephen D. Chernausek discussed the future of health care for patients with Turner syndrome and the role of patient advocates, doctors, and the performance of translational research in the current environment. He focused on both expanding the manner in which health care could be delivered across the spectrum of age, and the heterogeneity of clinical issues that girls and women face. Dr. Carolyn Bondy reviewed the most current clinical guidelines for the care of girls and women with Turner syndrome [Bondy and Turner Syndrome Study, 2007] with the future goal of updating these guidelines, especially in the area of cardiovascular imaging and prenatal diagnosis. Dr. David Sandberg focused on health care access and the barriers in the health care system, particularly in the areas of behavioral health and the transition from pediatric to adult care [Conway 2009; Devernay et al., 2009; American Academy of Pediatrics, 2011; Crowley et al., 2011]. Dr. Gary A. Lorigan presented the results of a survey that was submitted to the TSSUS membership. Of 4,147 potential respondents Dr. Lorigan received 385 responses from women living with Turner syndrome and 417 responses from parents/guardians. Their concerns included social and psychological issues as well as educational and vocational challenges. The major medical issues facing Turner syndrome patients included cardiovascular, endocrinological, and hearing problems. Dr. Philippe B. Bacheljauw presented the results of the work from a professional panel that discussed the important components of a regional Turner resource center and the logistics of how such centers might be structured with larger more established programs collaborating with local clinics. Dr. Nelly Mauras presented her study related to the type and route of administration of estrogen replacement in girls with Turner syndrome [Torres-Santiago et al., 2013] as both a model of the type of research that could be done by the TRN, as well as how the data might influence guidelines for future care. Dr. Rebecca Knickmeyer presented evidence that girls and women with Turner syndrome have critical differences in key components of neural circuits for social cognition and working memory [Knickmeyer, 2012]. Dr. David Hong pointed out that while intelligence is normal, and verbal skills are enhanced for those living with Turner syndrome, visual spatial skills, executive function, arithmetic, and social cognition are at risk [Green et al., 2014]. Dr. Siddharth K. Prakash presented the results of a genome-wide association study describing preliminary evidence that modifier genes are present on chromosomes 4, 18, and 22 that may account for the high frequency of bicuspid aortic valve in Turner syndrome. Dr. Carolyn Bondy presented a large body of work from the National Institute of Child Health

and Human Development natural history study which included nearly 500 girls and women with Turner syndrome, focusing on the congenital anatomic findings. There appear to be biological differences in rates of atherosclerotic heart disease between those women who carry a maternal X chromosome (increased risk) versus those with a paternal X chromosome (lower risk) [Abd-Elmoniem et al., 2014]. Dr. Paul Kruszka described work being done at the Medical Genetics Branch of the National Institutes of Health on the genetic underpinnings of congenital heart disease in Turner syndrome, including whole exome sequencing studies and the development of an animal model. Dr. Victoria Pemberton discussed the challenges of conducting human-based research in rare conditions.

Networks or “Collaboratories,” composed of multiple research centers, will be necessary to recruit adequate numbers of subjects for future research. Dr. David Cole discussed the challenges to funding an organization like the TRN in an era of diminished federal investment in medical science. A key to the TRN's success will be empowerment through the patients living with Turner syndrome and their families. An important strength of the TRN steering committee will be the direct participation of all the stakeholders, with patient advocates taking the lead.

Speakers' Abstracts

Health Care Policy and Health Care Delivery for TS Patients

The future of health care in the USA: Patient advocates, doctors, and translational research. Steven D. Chernausek, MD—Henry Turner, an internist, described the clinical features of Turner syndrome in 1938. Initially, medical care for patients with Turner syndrome focused on making the diagnosis, detecting associated anomalies, treating hypogonadism, and maximizing final adult stature. For the latter, low dose oxandrolone was given in late childhood with estrogen, replacement typically delayed until the age of 14 or 15 years to extend the growth period. In the 1980s the development of recombinant human growth hormone (rhGH) changed the approach to increasing height. Turner syndrome was the first non-growth hormone-deficient condition in which the efficacy of rhGH was formally examined with randomized, controlled trials, and treatment was subsequently implemented as standard of care. Concurrently, the endocrine community began to deal with Turner syndrome more comprehensively. In the last 10–15 years, the emphasis of care shifted from dealing with the growth deficit, to applying advanced reproductive technology allowing live births, detecting and dealing with potential catastrophic cardiovascular disease (CVD), and addressing long-term health issues. It is now apparent that there is significant excess mortality in adult women with Turner syndrome, half of which is attributed to CVD. While CVD complications typically manifest during adult life, the problems begin during childhood, and must be addressed first by pediatric endocrinologists and cardiologists, then transitioned to adult practitioners. Smooth transition from pediatric to adult care is key to maintaining appropriate surveillance for comorbidities and optimal delivery of health care to women with Turner syndrome. The challenge now is to incorporate the new approaches to clinical care, to deal with the problems of transition, and to apply the most modern genetic methodologies that will address important health concerns in this population.

Turner syndrome guidelines revisited. Carolyn Bondy, MS, MD—Since the 2007 NIH Consensus Conference on guidelines on diagnosis and care for patients with Turner syndrome, [Bondy and Turner Syndrome Study, 2007] major developments in genetic diagnosis and cardiac imaging technologies have emerged. Commercially marketed genomic testing kits claim detection of Turner syndrome and other chromosomal anomalies prenatally as early as 10 weeks of pregnancy. However, the American College of Obstetrics and Gynecology requires confirmation by standard prenatal cytogenetic testing [Genetics 2013]. The concern is that parental distress will lead to ill-informed terminations of early pregnancies. Current American College of Medical Genetics guidelines for diagnosis of Turner syndrome requires standard cytogenetic karyotype analysis. DNA-sequencing or DNA-array analyses from spot samples of saliva or blood suggest less laborious tests may be useful [Gregg et al., 2013]. More study is needed to demonstrate the reliability of these newer techniques. Advances in cardiovascular magnetic resonance imaging (cMRI) show that up to 25% of significant aortic abnormalities in Turner syndrome are not detectable by routine echocardiography. Thus, cMRI for all girls with Turner syndrome at an early age or at the time of diagnosis in older patients should be considered. Individuals who have aortic disease are at risk for complications, including aortic valve dysfunction and thoracic aortic dissection or rupture [Carlson et al., 2012]. It will be important to define which patients require close monitoring and counseling regarding safe levels of activity or attempting pregnancy. Treating toddlers with growth hormone (rhGH) may prevent growth from falling below the normal range and potentially reduce the duration and dosage of rhGH treatment. Treatment at a younger age may be important to optimize long-term height outcome. Because most of the data supporting the efficacy and safety of rhGH treatment in Turner syndrome derive from girls treated from approximately age 7, earlier treatment and/or longer duration need validation by additional controlled studies. Another area of active study is the timing of initiation of estrogen treatment, and the value of transdermal application of 17-beta estradiol versus varied forms of oral estrogen treatment.

Barriers to health care access for patients with Turner syndrome. David E. Sandberg, PhD—Turner syndrome is well described from a clinical standpoint. Clinical practice guidelines provide guidance regarding details of screening for problems at the time of diagnosis as well as the need for ongoing monitoring. The distinction between what is recommended and what is achieved is nowhere more apparent than in the coordination of the multiple specialty services involved in caring for those affected with Turner syndrome and their families. The barriers to delivering evidence-based comprehensive and integrated health care services can be classified as intra-institutional, extra-institutional, and cross-institutional (Table I). At the institutional level, integration, coordination, and continuity of care loom large as barriers to optimal health outcomes. Providers in an interdisciplinary team meet regularly to discuss and collaboratively set treatment goals for the patients and jointly carry out the treatment plans. A key barrier to interdisciplinary care is the lack of availability of certain specialties, in particular, behavioral health, either because of scarcity of this resource at the institution, or because of limited reimbursement. Extra-institutional barriers include factors such as the geographic location of interdisciplinary health care teams for Turner syndrome, generally found in tertiary care centers. Insurance coverage and its cost represent additional potential barriers to interdisciplinary team care. Although the U.S.

Patient Protection and Affordable Care Act of 2010 expanded health care coverage and prohibited the practice of excluding coverage for those with preexisting conditions, insurance providers may still restrict delivery of services to preferred in-network providers and facilities that are unable to assemble the expertise required for optimal care for patients with complex health care needs such as those with Turner syndrome. Furthermore, effective implementation of transition of health care services from pediatric to adult providers remains elusive.

Finally, “cross-institutional” barriers in this context refer to limited standardization in the process of diagnosis, description of the Turner syndrome phenotype and variability in clinical management practices across health care centers. Electronic health records offer the opportunity to enhance the process of standardization and reduce variability in practice. Movement in this direction not only provides the possibility to improve the quality of care and outcomes for the individual patient, but the standardization that would flow from such initiatives could also serve as a scalable platform for clinical research involving a national network of clinical teams focused on Turner syndrome.

Summary of advocacy panel poll of members of the Turner syndrome community, Gary A. Lorigan PhD

A survey was sent out to 4,147 members of the Turner syndrome community. The purpose of the survey was to answer the following three questions:

1. What are the major health and well-being issues facing girls and women living with Turner syndrome?
2. What is needed to ensure care for patients with Turner syndrome through the transition period into adulthood?
3. What are the barriers to better health and wellness for people living with Turner syndrome?

The survey's structure separated respondents into two categories: women with Turner syndrome and adults caring for girls with Turner syndrome under the age of 18. There were 385 responses from women 18–70+ years of age, and 417 responses from parents or guardians of girls with Turner syndrome under age 18. The four major medical concerns overall were endocrine, growth rate (for those under 18 years), cardiovascular, and hearing/ear. The major psychological/social issues were age-dependent, but included short stature, anxiety, educational challenges, poor motor skills, attention deficit, sexual function, low self-esteem, and social interactions. Other important issues included employment challenges, driving, and depression. The major health maintenance issues were lack of knowledgeable providers for needs of individuals with Turner syndrome, oversight of all healthcare components, and online access to resources for patients with Turner syndrome. For access to clinical care, the majority of respondents want a clinic no more than three hours away, which is a significant problem given the lack of existing centers or clinics for Turner syndrome across the U.S. Forty percent of the women with Turner syndrome surveyed wanted access to a specialized clinic/center, and 35% said that they wanted a primary care physician who was knowledgeable in health concerns related to Turner syndrome. About 50% of adult respondents said they would be willing to continue their care

in a pediatric facility if it ensured that care would come from a knowledgeable provider. The cost of health care and insurance were of concern to the majority of respondents. The surveys indicate the need for more research into issues and concerns related to Turner syndrome, better oversight of all aspects of healthcare, and the need for easy online access to information and resources for patients living with Turner syndrome.

Synopsis from the professional panel discussions regarding regional Turner syndrome resource centers. Philippe Backeljauw MD—A recent survey on the

status of Turner syndrome clinics in the U.S. revealed that approximately 20–25 healthcare institutions identified the existence of such a subspecialty clinic. The size and length of time these clinics have been in existence varies considerably. Some of the institutions support a true Turner syndrome center and are able to provide state-of-the-art care through the involvement of multiple specialties, as well as via the interaction with patient support groups. Only a few are also able to care for adults with Turner syndrome. The major health and well-being issues and challenges currently facing girls and women with Turner syndrome from a care provider perspective include:

1. Proper transition of pediatric patients to adult care;
2. Education regarding co-morbidities and preparedness for adult care/life for patients with Turner syndrome, including reproductive issues;
3. Access to appropriate developmental, psychological and psychiatric evaluation and therapy;
4. Obtaining adequate health insurance coverage.

Several barriers to improving health and wellness for patients with Turner syndrome have been identified:

1. Lack of follow-up care;
2. Lack of coordination of subspecialty care;
3. Difficulty in identifying knowledgeable (adult) providers;
4. Lack of uniform criteria for lifelong screening and care for patients with Turner syndrome.

The professional panel envisions several regional, comprehensive clinical centers. This could potentially lead to an integrated national TS care network. An educational component could be part of the TS clinic activities with patients and their families and local TS support groups collaborating to increase TS awareness and provide counseling. TS research could be integrated into a TRN, through which the smaller TS clinics could feed into larger TS resource centers. Quality improvement projects could be developed, as well as novel pilot research studies and multi-center studies.

Turner Science: from Genotype to Phenotype

Estrogen Replacement in Adolescents With Turner Syndrome. Nelly Mauras, MD

The proper timing, dose and more recently, route of estrogen replacement in hypogonadal girls with Turner syndrome have been better characterized in recent studies. Although historically, conjugated equine estrogens (CEE) had been the typical method of estrogen replacement for patients with Turner syndrome and other hypogonadal states in the U.S., CEE contains over 100 forms of estrogens of different potencies and biological activity. Estradiol ($17\beta E_2$) is the most physiological estrogen available for replacement as it is identical to the product of the intact gonad. It also has the advantage that it can be accurately measured in plasma. Micronized $17\beta E_2$ should be the preferred choice for feminizing girls with different forms of hypogonadism. Most studies of the metabolic effects of the different routes of estrogen administration have used different types of estrogen, making comparisons across studies difficult. We recently studied the metabolic effects of the same form of estradiol, $17\beta E_2$ administered either orally or transdermally, in a group of 40 girls with Turner syndrome in whom we titrated the doses based on E_2 concentrations obtained monthly, measured by liquid chromatography—mass spectroscopy. We aimed to achieve levels comparable to those of normally menstruating adolescents measured in the same assay in both groups. All subjects were cycled with progesterone monthly. After 12 months of treatment, there were no differences between the groups for E_2 concentrations, body composition, lean body mass, adiposity, bone mass accrual or energy expenditure, LH/FSH suppression or lipid concentrations. IGF-I concentrations trended lower in the transdermal group, but still remained within normal range. However, there were considerable differences in the levels of estrone, estrone sulfate and total bioestrogen concentrations (measured using a recombinant cell bioassay), with levels much higher in the oral group, creating an unphysiologic estrogen milieu. Both estrone and estrone sulfate can be stored in the adipocyte and breast tissue and recycled back into E_2 creating a reservoir of estrogen in the body. These results are important, given the compelling body of data that have accumulated on the increased thromboembolic effects of oral over transdermal estrogens in both post- and pre-menopausal women. Whether transdermal estrogen produces a greater accumulation of other estrogen metabolites that can cause DNA damage (genotoxic estrogens) awaits further study. We concluded that adolescent girls with Turner syndrome should be feminized at the normal physiologic time, preferably using transdermal $17\beta E_2$ which produces a more physiologic milieu. The therapeutic guidelines for estrogen replacement therapy in Turner syndrome need to be revised.

Early Abnormalities in Social, Attentional, and Working Memory Circuits in Infants With Turner Syndrome. Rebecca Knickmeyer, PhD

Adults and children with Turner syndrome differ from typical female individuals with 46,XX karyotype in key components of neural circuits for social cognition and working memory. Specifically, imaging studies demonstrate reductions in somatosensory cortex and inferior parietal lobule, enlargement of the amygdalae and insular and orbitofrontal cortex, altered white matter microstructure and disrupted frontoparietal circuitry in women with Turner syndrome. Altered activation of the amygdala and caudate during cognitive tasks also has been reported. What is not known is when in development these relationships arise.

This knowledge gap is important, as it limits our ability to determine the appropriate type and timing of behavioral interventions and hormone therapies. Imaging of infants with Turner syndrome showed decreased gray matter volumes in parietal cortex and increased gray matter volumes in insular cortex when compared to female controls, consistent with findings in older children. This suggests a stable phenotype, with origins in the prenatal or early postnatal period. Infants with Turner syndrome did not exhibit widespread changes in white matter microstructure that have been reported in older children, suggesting that early interventions might prevent or ameliorate atypical white matter development in Turner syndrome. At 1 year of age, functional connectivity maps revealed reduced fronto-parietal connectivity in infants with Turner syndrome, and increased connectivity with the insula. At age 2, functional connectivity maps revealed a lack of typical connectivity between caudate and frontal lobe in infants with Turner syndrome. Extensive negative correlations with middle temporal gyrus were present in infants with Turner syndrome, but not in controls. Additional studies are needed to examine longitudinal changes in brain structure and function in Turner syndrome, relate clinical variables (such as genetic and hormonal variation) to brain development, and test whether individual variation in neuroimaging phenotypes predicts cognitive outcomes.

Genetic and Epigenetic Mechanisms Underlying Early Brain Development, Cognition, and Behavior in TS. David S. Hong, M.D

Significant concerns for parents and individuals with Turner syndrome are the potential cognitive issues associated with this condition. Neuropsychological, genetic and neuroimaging studies indicate that overall intelligence in Turner syndrome is within the normative range. However, specific cognitive sub-domains may represent areas of risk, including visuospatial skills, executive function, arithmetic and social cognition, while others may be relatively enhanced, such as verbal skills. Significant gaps in current understanding of cognitive aspects of Turner syndrome still remain, particularly in regard to the correlation between older neuropsychological findings and more recent genetic and neuroimaging data, as well as a clearer view of the trajectory of cognitive development in Turner syndrome over the lifespan. Recent studies may provide further insight into developmental issues related to Turner syndrome, including the first concrete evidence for aberrant longitudinal trajectories of neurodevelopment, confirming the critical need for using lifespan studies to better delineate dynamic changes in brain growth patterns across various stages of development. It is important to understand how these brain findings relate to long-term adaptive outcomes. Understanding the genotype-phenotype relationships between genes on the X chromosome and brain development is also important. Findings include evidence of imprinting, an epigenetic mechanism related to parental origin of genetic material. Girls who have 45,X karyotype with a paternally-derived X chromosome perform less well in the performance IQ domain relative to peers with a maternally-derived X chromosome, a finding which may reflect a neurobiological basis for observed cognitive differences between these two cohorts. Additionally, X chromosome “dosage” may have a specific effect on brain development, with the number of sex chromosomes linearly correlated to brain volumes in the temporal and parietal lobes. In totality, advances in neuroimaging and genetic technologies over the past decade have significant potential to

exponentially increase our understanding of cognition and neurodevelopment in Turner syndrome.

Genetic Basis of Bicuspid Aortic valve in Turner Syndrome. Siddharth K. Prakash, MD, PhD

Bicuspid aortic valve (BAV) is the most common congenital heart defect. BAV is caused by the failure of two or more cusps to separate during late stages of embryonic development. The prevalence of BAV is increased more than 30-fold in women with Turner syndrome, who are at greatly increased risk for acute aortic dissections. Girls and women with Turner syndrome require operations for significant left heart obstructive disease far more than those without the condition. We hypothesize that at least two genetic hits are required for susceptibility to aortic disease in Turner syndrome. The first hit may be a reduction in the dosage of X chromosome genes due to X chromosome structural variation in Turner syndrome. A second hit could be a common variant or a modifier allele that does not cause disease by itself but may interact with reduced X chromosome dosage to account for the prevalence of BAVs in women with Turner syndrome. To test our hypothesis, we performed a genome-wide association study in women with Turner syndrome comparing those with BAV to those with normal tricuspid aortic valves. We observed suggestive association peaks on chromosomes 4, 18, and 22, with a minimum P -value of 1×10^{-7} . We also confirmed that BAV is strongly associated with the dosage, but not the genotypes of single nucleotide polymorphisms on the short arm of the X chromosome (Xp) and used breakpoint mapping to identify several new candidate Xp genes for BAV. These findings are consistent with our hypothesis that BAV may be caused by reduced X chromosome dosage in women with Turner syndrome, as well as men in the general population, and opens new avenues for BAV gene discovery.

Insights into Congenital and Ischemic Heart Disease From Studies in Turner Syndrome. Carolyn Bondy, MS, MD

Five hundred girls and women with rigorously established Turner syndrome karyotypes were examined with cardiac MRI as well as transthoracic ultrasound. These imaging studies show that approximately 50% of study subjects had an abnormal elongation of the transverse portion of the aortic arch (ETA). This anomaly is associated with a distinctive kink in the lesser curvature and bulbous dilation of the left subclavian artery origin in the region usually involved in aortic coarctation. The specific anatomic alterations of defective aortic valve and aortic coarctation were exclusively found among those with ETA. While the bicuspid aortic valve was found in 30% of the general study population, it was found in 60% of those with the ETA, suggesting that haploinsufficiency for unknown X/Y chromosomal gene(s) caused abnormal aortic arch development, which secondarily led to defective aortic valve development, and likely also to aortic coarctation, possibly due to severely abnormal blood flow patterns in the developing aortic arch. This possibility is supported by the finding of severe abnormalities of the transverse arch (interruption or tubular hypoplasia) in 45, X fetuses or newborns that succumbed to cardiovascular defect. Genetic studies of the congenital cardiovascular phenotype mapped the phenotype to the short arm of the X chromosome, telomeric to Xp.11.4 (and homologous gene(s) present on Yp). Congenital defects were equally prevalent in groups with a single X chromosome derived from the

mother or the father, indicating that genomic imprinting does not contribute to the risk for congenital cardiac defects in Turnersyndrome. We investigated deposits of calcium in the coronary arteries of groups monosomic for a maternal versus paternal X chromosome, and found that the coronary calcium was abundant in women with a maternal X (similar to age-matched population men from the Framingham study) and totally absent from the coronaries of women with a paternal X, suggesting that the presence of a single maternal X chromosome is an independent risk factor for atherosclerotic coronary disease.

Genomic Approaches to Understanding Congenital Cardiac Anomalies in Congenital Heart Disease (CHD) in Turner Syndrome, Paul Kruszka, MD

Congenital heart disease occurs in almost half of girls and women with Turner syndrome and is a leading cause of morbidity and mortality. Bicuspid aortic valve occurs in over 30% of individuals with Turner syndrome and aortic coarctation occurs in approximately 12%. Aortic dissection, the most catastrophic anomaly, is increased more than 100-fold in Turner syndrome. Previous studies suggest that a genetic culprit is located on the short arm of the X chromosome (X_p); however, a single gene, or group of genes, causing CHD in Turner syndrome have yet to be found. The most popular hypothesis is that haploinsufficiency of the pseudoautosomal region (PAR1) genes or other genes on X_p that have homologues on the Y chromosome contribute to the cause of CHD. Unfortunately, an adequate animal model for CHD in Turner syndrome does not exist, as the XO mouse does not have heart defects.

Maximilian Muenke at the National Human Genome Research Institute, the National Institutes of Health (NIH) is conducting whole exome sequencing in girls and women with Turner syndrome in an effort to better understand the genetic and molecular underpinnings of cardiac disease in this condition. Additionally, new gene editing techniques and animal models of Turner syndrome are being developed to couple gene discovery in humans with functional analyses. This multidisciplinary approach to research in Turner syndrome is directed at developing mechanistic insights into CHD in the condition and provides an avenue for the development of new diagnostic and therapeutic capabilities in the future.

Crossroads of Health Policy and Research: Roadmap Toward the TRN

Securing a National Turner Syndrome Program in an Era of Declining Federal Resources. David A. Cole, PhD

Building a robust TRN is a worthy goal, but one that will require substantial financial resources—resources in excess of those currently raised by the Turner Syndrome Society (TSSUS) and the Turner Syndrome Foundation (TSF) combined. The TRN will face challenges in the form of several key scientific and philanthropic trends: a) NIH and National Science Foundation grant making, especially for basic scientific investigation, is falling victim to federal budget cutting; b) corporate grant making is on the decline and increasingly tied to companies' marketing objectives; c) corporate and foundation grant makers are allocating fewer dollars for indirect cost recovery; d) the time required to apply for, and steward, institutional grants is increasing; and e) grant makers are fielding record numbers of applications and making smaller grants. One additional philanthropic trend,

however, suggests another, more promising approach: substantial sums, allocated by individuals for philanthropy, are increasingly being channeled into private foundations and donor advised funds (DAFs). TSSUS and TSF should consider pooling their resources and investing in a major gifts fundraiser. The centrally coordinated resources of TSSUS/TSF could be directed toward the following activities: 1) leveraging existing ties to TSS/TSF supporters and members to identify, and build new relationships; 2) developing a major gifts “moves management” function within TSSUS/TSF to coordinate prospect identification, cultivation, applications, and gift/grant stewardship on a national level. This function would ensure that fundraising steps are centrally managed and communicated across the TRN network; 3) ensuring that TSSUS/TSF establish and maintain a major gifts focus on their common website, on social media, and in related communications collateral

Successful Models for Conceiving, Implementing, and Conducting Multi-Center Research. Victoria Pemberton, RNC, MS

Like other rare diseases, clinical care and research in Turner syndrome faces similar challenges related to the small number of affected individuals seen at any given institution; heterogeneity of care practices, and physicians' and patients' limited experiences of participating in research. Networks or “Collaboratories,” composed of multiple research centers, are likely necessary for the effective conduct of clinical research with adequate numbers of patients to meet sample size requirements. Key elements for a successful TRN were identified and include standardization of research procedures, multidisciplinary working relationships, shared learning regarding mistakes and successes, open access to researchers with important study proposals, integrating research with clinical care, and central monitoring and oversight. The TRN must nurture partnerships with patient advocacy groups as these groups serve as conduits for education among their members about the importance of research, they provide insight into potential study questions, highlighting those that are most critical to individuals with Turner syndrome, and they provide support and resources such as potential research participants, educational information, financial support, and political advocacy on behalf of the TRN. An effective infrastructure must consider leveraging funding opportunities with government agencies, pharmaceutical companies, foundations, advocacy groups and investigators with similar interests. An important mission for the TRN will be to discern the “extended opportunities” that can lead to therapies and interventions for both Turner syndrome and other populations.

TRN Roadmap Synopses (6 breakout sessions)

How the Turner resource network steering committee should be organized—

There should be a start-up steering committee, a working group tasked with calling for proposals, establishing criteria for the regional centers, and developing policies and procedures for how the network would operate. The group should be multidisciplinary and should also have family advocates/women living with Turner syndrome represented. The group must represent all of the diversity of opinions and thoughts within the TRN.

How will the TRN patient-powered registry be designed?—How the information will be accessed needs to be determined. The registry committee should include families and lay advocates alongside clinicians and researchers. This group will decide the areas of focus,

what important outcomes should be, the types of data that should be collected, and how the information will be used. The existing NHLBI-sponsored National Registry of Thoracic Aortic Aneurysms and Related Conditions (GenTAC) contains over 300 subjects with Turner syndrome for whom extensive cardiovascular data, both cross-sectional and longitudinal, have been collected [Kroner et al., 2011]. When the TRN registry incorporates the GenTAC Turner data it will be research ready. An application to the PCORI patient-powered research network (PPRN) [Daugherty et al., 2014] is planned. Transparency regarding how the Turner database can be used for research purposes will be necessary. Key questions without necessarily supplying specific answers were posed: What kind of data beyond the GenTAC cardiovascular component will be collected—longitudinal or cross-sectional, retrospective or prospective? What domains of data general health, genetics, phenotype, and demographics need to be included? Should the data be comprehensive, agnostic or hypothesis-driven? Will it serve as a resource to both “TRN investigators” and outside individuals or organizations? What areas of data will be collected in a standardized fashion? Possibilities include: endocrine including reproductive endocrine, cardiovascular, genetics, and neurobiological, including cognition? Will the coordinating center serve as bio-repository of genetic data, imaging data? Will the coordinating center serve as bio-repository of genetic data, imaging data? A group volunteered to further consider the question going forward.

How will the Turner resource network be funded?—Without the aligned support of the three major advocacy groups, the Turner Syndrome Society of the United States, the Turner Syndrome Foundation and the Turner Syndrome Global Alliance, the TRN will not succeed. It is through the membership of these organizations that avenues for philanthropic support will become apparent. Perhaps needed services, informatics/database support, can be obtained by soliciting contributions from a large group of people, and especially from an online community (“crowdsourcing”) may be an option. Employing a professional skilled in philanthropic activities will be necessary. Funding opportunities from all potentially receptive health organizations will be explored. In particular, requests for applications to the Patient Centered Outcomes Research Initiative (PCORI) will be primarily considered.

What is the ideal regional resource center?—The focus should be the regional Turner syndrome clinic. The key to success for these clinics is coordination of care for the individual living with Turner syndrome. A successful clinic will be a platform through which research can be performed. The clinic will require designated standards and some measures to evaluate each clinic's success. Primary care coordination will require at the very least, cardiology, endocrinology, and neuro-developmental expertise. The action item is to publish the current matrix of 25 Turner regional centers collated by Dr. Angela Lin, and to develop a working group to establish the criteria for designation as a regional resource center.

Which Turner syndrome guidelines need to be revisited?—The guidelines overall should be updated. Consideration should be given to publishing guidelines on a specific subtopic as a way of tackling the larger issue of guidelines updates. Consideration should be given to taking an age-related life span approach (fetus, infant, child, adolescent, and adult).

Lay versions of the guidelines should be created. There are a number of pressing specific questions: Which sex steroid replacement therapies and the timing, dosage and other issues of sex steroid therapy need to be clarified? Turner syndrome diagnosis options and their utilization/timing need to be defined (karyotype vs. microarray, newborn screening).

Timing and need for other medical screening tests need to be clarified. The indications for echocardiography versus MRI for cardiovascular disease are unclear. Dosing and timing of rhGH therapy recommendations should be studied further. What are the indications, contraindications, and relative contraindications for pregnancy? What screening tests are needed prior to pregnancy? A pregnancy consent form should be considered as a way to precipitate a thorough discussion about potential risks. Guidelines for fertility preservation need to be established. Indications for cognitive assessment and their relative value are unclear.

How will the Turner resource network research project be reviewed?—Funds within the TRN will be available for research projects. In addition, investigators with their own funds will wish to take advantage of TRN resources for Turner syndrome-related projects. The major factor determining research priorities overall will be the best science that meets the priorities as set by the TRN scientific advisory committee.

Conclusions

Morbidity and mortality in Turner syndrome is unacceptably high. The TRN needs to help find ways to improve health policy and health care delivery for girls and women living with Turner syndrome by: 1) creating nationally coordinated regional resource centers linked by a patient-powered registry; 2) conducting high quality outcomes-based clinical research; and 3) supporting basic Turner science programs. The research community in general needs to step up in terms of efforts to understand sex-chromosome biology, its deep biology in all of its complexity, so that we can better understand the clinical and personal ramifications of living with Turner syndrome. We must also elucidate the role of the X chromosome in common disease susceptibility in the general population. A concerted effort by the NIH, national medical/scientific foundations and societies, as well as the pharmaceutical industry is necessary to bring the sex chromosomes back to the forefront of research. The TRN can encourage and promote this process by engaging in research in Turner syndrome.

Acknowledgments

We thank all the organizers, families, and professionals who attended the symposium, for contributing their time and opinions that made the meeting a success. This work was supported in part by grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (1R13HD079209-01), The Office of Women's Health Research, The American Heart Association, The March of Dimes, The Leaping Butterfly Ministry, and the Turner Syndrome Society of the United States.

Grant sponsor: Eunice Kennedy Shriver National Institute of Child Health; Grant number: 1R13HD079209-01; Grant sponsor: The March of Dimes; Grant sponsor: The American Heart Association; Grant sponsor: The Office of Women's Health Research; Grant sponsor: Leaping Butterfly Ministries; Grant sponsor: The Turner Syndrome Society of the United States.

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Fig. 1. Cumulative risk of death from all causes and from circulatory disease observed in the cohort of patients with Turner syndrome and risk expected based on general population rates for females (reproduced with permission Schoemaker and other 2008)

Table I
Selected Barriers to Full Implementation of Turner Syndrome Clinical Practice Guidelines

Internal	External	Cross-institutional
integration/coordination	location	standardization
“team” care	cost/insurance	practice guidelines
behavioral health	transition	

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