JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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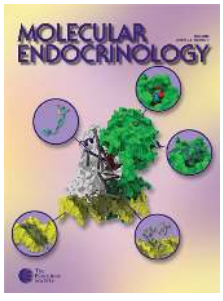
J. Clin. Endocrinol. Metab. 2007 92:804-810 originally published online Jan 2, 2007; , doi: 10.1210/jc.2006-2017



0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(3):804–810

doi: 10.1210/jc.2006-2017

CONSENSUS STATEMENT: Management of the Child Born Small for Gestational Age through to Adulthood: A Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society

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Objective: Low birth weight remains a major cause of morbidity and mortality in early infancy and childhood. It is associated with an increased risk of health problems later in life, particularly coronary heart disease and stroke. A meeting was convened to identify the key health issues facing a child born small for gestational age (SGA) and to propose management strategies.

Participants: There were 42 participants chosen for their expertise in obstetrics, peri- and neonatal medicine, pediatrics, pediatric and adult endocrinology, epidemiology, and pharmacology.

Evidence: Written materials were exchanged, reviewed, revised, and then made available to all. This formed the basis for discussions at the meeting. Where published data were not available or adequate, discussion was based on expert clinical opinions.

Consensus Process: Each set of questions was considered by all and then discussed in plenary sessions with consensus and unresolved issues identified. The consensus statement was prepared in plenary sessions and then edited by the group chairs and shared with all participants.

Conclusions: The diagnosis of SGA should be based on accurate anthropometry at birth including weight, length, and head circumference. We recommend early surveillance in a growth clinic for those without catch-up. Early neurodevelopment evaluation and interventions are warranted in at-risk children. Endocrine and metabolic disturbances in the SGA child are recognized but infrequent. For the 10% who lack catch-up, GH treatment can increase linear growth. Early intervention with GH for those with severe growth retardation (height SD score, <-2.5; age, 2–4 yr) should be considered at a dose of 35–70 μg/kg·d. Long-term surveillance of treated patients is essential. The associations at a population level between low birth weight, including SGA, and coronary heart disease and stroke in later life are recognized, but there is inadequate evidence to recommend routine health surveillance of all adults born SGA outside of normal clinical practice. **(*J Clin Endocrinol Metab* 92: 804–810, 2007)**

LOW BIRTH WEIGHT remains a major cause of morbidity and mortality in early infancy and childhood throughout the world (1). In addition, being born small has been associated with increased mortality from a wide range of disorders, in particular coronary heart disease (CHD) and stroke (2). For children born small for gestational age (SGA), it is important to integrate such data into their health-care management. Therefore, a meeting was convened in Manchester, United Kingdom, in February 2006, with representation from pediatric endocrine societies and the Growth Hormone Research Society, to examine current data relevant to the early, mid-, and long-term outcome of children born SGA. This statement presents a summary of key health issues and proposed management of these children while recognizing topics that require further investigation.

First Published Online January 2, 2007

Abbreviations: AGA, Appropriate for gestational age; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HPA, hypothalamic-pituitary-adrenal; IUGR, intrauterine growth retardation; SDS, SD score; SGA, small for gestational age.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Definition

The definition of SGA is not straightforward. It requires the following: 1) accurate knowledge of gestational age (ideally based on first trimester ultrasound exam), 2) accurate measurements at birth of weight, length, and head circumference, and 3) a cutoff against reference data from a relevant population. This cutoff has been variably set at the 10th centile, 3rd centile, or at less than -2 SD from the mean ($\sim$2nd centile) (3). We recommend that SGA should be defined as a weight and/or length less than -2 SD because this will identify the majority of those in whom ongoing growth assessment is required.

Babies can then be subclassified into SGA for weight, SGA for length, or SGA for both weight and length (3). Additionally, those SGA babies who have small head circumference should be recognized. This subclassification may help in understanding the mechanisms and implications of being born SGA.

With knowledge of intrauterine growth performance, it is possible to identify intrauterine growth retardation (IUGR; slow fetal growth based on two ultrasound measurements), which may result in a SGA baby. IUGR babies irrespective of birth size may require ongoing surveillance.

Definition of SGA does not take into account background growth-modifying factors such as maternal size, ethnicity, and parity. These modifying factors can be used in statistical computations to generate a corrected birth weight, which increases the chance of correctly identifying a baby with abnormal fetal growth (4). Application of this method to those with modest growth restriction (birth size between the 3rd and 10th percentiles) may allow identification of pathological growth within this group. Infants identified in this way have a higher risk of perinatal morbidity than those identified by an anthropometric definition. The concept of a customized individual growth assessment has merit in the perinatal period but as yet has an unproven role in identification of those at risk of long-term morbidity.

Identification of the SGA and/or IUGR baby is important because these infants are at an increased risk for perinatal morbidity, associated health problems (such as neurodevelopmental disorders), persistent short stature, and metabolic alterations in later life.

Early Growth and Development

Growth

Children born SGA are shorter during childhood and as adults, reaching adult heights that on average are approximately 1 SD lower than the mean (5, 6). The typical infant born SGA experiences a period of accelerated linear growth during the first 12 months of life that results in a stature above −2 SD in up to 90%. Most of the catch-up growth occurs during the first year and is near completion by 2 yr of age (5, 7). Those born very prematurely and with more severe degrees of growth retardation, especially reduced birth length, are less likely to reach a stature within the normal range, whereas those with taller parents are more likely to reach a normal adult height (8). Catch-up growth may be incomplete in recognized syndromes, such as Silver Russell or 3M. Neither circulating concentrations of GH, IGF-I, IGF-binding protein-3 nor ponderal index are predictive of subsequent growth (9). The relationship between etiology of fetal growth retardation and postnatal growth pattern is not extensively delineated.

We recommend that a child born SGA should have measurements of length, weight, and head circumference every 3 months for the first year of life and every 6 months thereafter. Those individuals who do not manifest significant catch-up growth in the first 6 months of life or those who remain short by 2 yr of age may have other conditions that limit growth. These should be identified and managed.

The preterm infant is a special case. The preterm SGA infant can take four or more years to achieve a height in the normal range (10). The preterm infant born appropriate for gestational age (AGA) often grows slowly in the first weeks, and the risk of this is increased with increasing prematurity (11). These infants are small at expected date of delivery.

Body composition

Individuals born SGA have low lean mass and may have increased central adiposity. Dual-energy x-ray absorptiometry is the definitive investigation to assess body composition and is used for research purposes. Body mass index (BMI) is used for clinical purposes but is of limited value in defining body composition in SGA children because of its poor prediction of lean tissue and fat compartments.

Birth weight is weakly positively associated with later BMI (12), whereas rapid weight gain in infancy is associated with increased incidence of obesity in later life (13, 14). Two systematic reviews have shown that breast feeding in infancy may protect against the long-term risk of developing obesity (15, 16). However, neither specifically addressed SGA infants. Nevertheless, in view of these data, calorie-dense feeding for SGA infants may not be appropriate.

Neurological and intellectual consequences

In large observational studies, cognitive impairment is independently associated with low birth weight, short birth length, and small head circumference for gestational age. The effect is moderate but significant. Those without catch-up in height and/or head circumference have the worst outcome (17, 18). Being born SGA is associated in particular with lower cognitive ability in mathematics and reading comprehension and with more emotional, conduct, and attention deficit hyperactivity disorders. In view of these data, early neurodevelopment evaluation and interventions are warranted in at-risk children.

Long-term exclusive breastfeeding (24 wk or more) may prevent some of the intellectual impairment (19). GH treatment induces catch-up growth in head circumference particularly in those with small head circumference at birth. There is some evidence that GH also improves IQ in short SGA children, but additional data are required (20). Long-term outcome data for children born SGA show no difference in frequency of employment, marital status, or satisfaction with life. However, these individuals hold fewer professional or managerial jobs and have significantly lower income than individuals of normal size at birth (21).

Endocrine Consequences

Intrauterine endocrine programming

There is experimental evidence in animal models for the presence of intrauterine programming of growth, weight gain, puberty, and metabolic and endocrine function (22). However, in humans, the evidence for programming is limited (23).

GH-IGF axis

The GH-IGF axis has been extensively studied in SGA children. Classic GHD is rare in this population. However, alterations in diurnal GH secretion patterns have been observed but are of limited diagnostic and prognostic utility (24, 25). Mean IGF-I and IGF-binding protein-3 levels are reduced in SGA children by approximately 1 SD, but the range of levels is wide, indicating possible heterogeneity in the mechanisms of growth failure from insufficient IGF-I

generation to IGF-I insensitivity (26–28). The status of the GH-IGF axis at birth or in early postnatal life is not predictive of later growth, and therefore hormone measurements in the SGA infant or child are not indicated in routine care (9).

However, in the short SGA child, assessment of the GH-IGF-I axis may be required if growth velocity is persistently reduced and signs of GH deficiency or hypopituitarism are present. Genetic abnormalities and polymorphisms in the GH-IGF axis have been associated with small size at birth and reduced postnatal growth. These include IGF-I and IGF-I receptor gene deletions, point mutations, and polymorphisms (29–32). However, current diagnostic utility of genetic analysis is limited. Additional research is needed to identify other candidate genes such as insulin and IGF-II.

Hypothalamic-pituitary-adrenal (HPA) axis

In animal models of prenatal stress, maternal malnutrition and maternal corticosteroid therapy have produced low-birth-weight offspring with basal and stimulated HPA hyperactivity and life-long hypertension and glucose intolerance (33, 34). Studies in humans to date suggest that there is no lasting effect of prenatal glucocorticoids on function of the postnatal HPA axis. Therefore, assessment of the HPA axis in the SGA child is not recommended.

Puberty and adrenarche

Most children born SGA have pubertal timing within normal limits (35). However, some studies in boys and girls born SGA indicate that pubertal growth is modestly decreased, whereas in girls, menarche occurs 5–10 months earlier than normal. These aberrations may result in a reduced adult stature (36, 37). In those who do have early puberty, there is typically a rapid progression through puberty leading to loss of adult height (38, 39). The variations in pubertal timing and progression recognized in the SGA child are likely to be related to many factors, including ethnicity, background population trends, nutrition, and other unknown influences.

SGA girls who display rapid weight gain during early childhood are more likely to have premature adrenarche (40–43). Puberty and menarche in SGA girls with premature adrenarche can be earlier than in AGA girls with premature adrenarche (44). Adrenarche onset is not different from the general population in children born SGA who do not catch up in height and weight.

Bone age is a poor predictor of pubertal timing and of adult height in SGA children (45). Its assessment is not recommended during routine follow-up.

In boys born SGA, hypospadias and cryptorchidism are more common (46).

Ovarian function

There are no substantial data to support ovarian dysfunction, reduced fertility, or early menopause in those born SGA (47, 48). However, some adolescents who were born SGA may have reduced ovulation rates, increased secretion of adrenal and ovarian androgens, excess abdominal fat (even in the absence of obesity), and hyperinsulinemia (47, 49). In these young women with evidence of clinical androgen excess, investigation in a standard manner is recommended. This variation in the frequency of polycystic ovary syndrome in women born SGA may be due to ethnic and geographic background and variation in the definition of the syndrome.

Thyroid and bone metabolism

There is currently no evidence for major alteration of the thyroid axis (27). In relation to bone health, being born SGA has been associated with reduced bone mineral content and bone mineral density, but the association is greatly reduced once adjusted for adult height (50). Low birth weight is not a significant predictor of fractures in adults (51).

Metabolic Consequences

Definition and assessment

Metabolic syndrome or the insulin resistance syndrome is a cluster of metabolic abnormalities characterized by insulin resistance/hyperinsulinemia, abnormalities in glucose metabolism, dyslipidemia, hypertension, and obesity (52). As in adulthood, there is no consensus regarding the definition of the metabolic syndrome in childhood.

Although the ideal means of evaluating insulin resistance is the hyperinsulinemic-euglycemic clamp, practical means of monitoring metabolic risk factors include measurement of blood pressure (BP), BMI, fasting glucose, and lipids. The measurement of fasting insulin is not recommended for clinical care because of the absence of accepted criteria to differentiate normality from abnormality. There are no established definitions in childhood for normal body composition, but BMI is the best clinical surrogate. Reference data are available from the International Obesity Task Force, the Centers for Disease Control, and other regional data.

Metabolic status in childhood, adolescence, and young adulthood in those born SGA

In children born SGA, insulin resistance may be present as early as 1 yr (53), and in prepubertal children, this is more evident in those with rapid weight gain and a BMI of at least 17 kg/m^2 (54, 55). Limited studies in SGA adolescents and young adults have shown that insulin-mediated glucose uptake is lower than in individuals with normal birth weight (6, 56), whereas those born SGA who develop high BMI in childhood are at increased risk of developing abnormal glucose metabolism in adulthood (57). Young adults born SGA have a higher incidence of metabolic risk factors (2.3%) than those born AGA (0.4%) (58). Nevertheless, the overall prevalence of risk factors is very low.

There is, however, no evidence that type 2 diabetes mellitus, impaired glucose tolerance, or dyslipidemia occurs more commonly among children born SGA than in the normal childhood population (59). There is a small effect of SGA on BP, primarily systolic, but no increased risk of childhood or adolescent hypertension (59, 60).

Although in well-established cohorts (61–63), there is evidence of tracking of metabolic risk factors from childhood to adulthood, there are no such data specifically for SGA children. As in the general childhood population, obesity and accelerated weight gain are likely to be major risk factors.

Neither the prevalence of SGA in childhood obesity nor the prevalence of obesity in SGA is known.

It is recognized that any risk for metabolic disorders associated with SGA can be amplified by the presence of other risk factors, such as weight gain, ethnicity, and family history. Nevertheless, routine evaluation of metabolic parameters is not justified in all children born SGA. Management of obese SGA children should occur in line with general pediatric practice, including lifestyle interventions.

Endocrine Management: Growth and Puberty

Early evaluation of short children born SGA is recommended, and those under 2 yr of age with a current length below −2.5 SD should be referred for evaluation. Short children born SGA form a heterogeneous group with various etiologies, and treatment should be preceded by an effort to identify the diagnosis.

The use of GH in short children born SGA has been explored for nearly 40 yr (64–66). This has led to official indications by the Food and Drug Administration in 2001 and by the European Agency for the Evaluation of Medicinal Products in 2003 (Table 1).

Factors associated with the response to GH over the first 2–3 yr include age and height SD score (SDS) at start of treatment, midparental height, and dose. Average height gains after 3 yr of GH treatment range from 1.2–2.0 SD for doses of 35–70 μg/kg·d. After the initial catch-up, most of this height gain is maintained up to adult height. The maintenance phase of GH treatment seems to be less dose dependent (66). Children with a recognized syndrome respond less well to GH than those with nonsyndromic SGA (66).

The discrepancies between the two approved indications are recognized (67). It is proposed that SGA children aged between 2–4 yr who show no evidence of catch-up with a height less than −2.5 SD should be eligible for GH treatment. In addition, for those SGA children over 4 yr old who are showing no evidence of catch-up, there was discussion about whether the cutoff for GH treatment should be at a height SDS of less than −2 or less than −2.5. No consensus was obtained, although a majority was in favor of initiating treatment at a height SDS of less than −2. With regard to GH dose, it is proposed that the starting dose should cover the range 35–70 μg/kg·d, with the higher doses used in those with the most marked growth retardation.

In the majority of short SGA children treated with GH during childhood, pubertal development begins on time and progresses normally (68). At present, there is no convincing evidence that the addition of GnRH analog treatment to inhibit pubertal progression is associated with additional height gain.

There should be a positive response to GH treatment (height velocity SDS more than +0.5 in the first year of treatment). If there is an inadequate response, reevaluation is indicated, including consideration of compliance, GH dose, diagnosis, and the decision to discontinue treatment. In those with a positive response to GH, withdrawal of GH therapy after 2–3 yr leads to catch-down growth and is not recommended (66). Discontinuation of GH treatment in adolescence is recommended when the growth rate falls to less than 2 cm/yr.

Pretreatment IGF-I levels may have a role in predicting responsiveness to GH (69), whereas in those children receiving GH, IGF-I monitoring as a tool for dose optimization may be useful. In all other respects, standard monitoring of GH therapy should be applied (70). Some syndromes (*e.g.* Bloom and Fanconi) may carry a specific risk, which may contraindicate GH treatment.

Treatment-emergent adverse events are not more common in this population than in other conditions treated with GH, nor have additional safety concerns arisen (71). It is currently unknown whether GH therapy for the SGA subject through childhood and adolescence is associated with benefits or amplification of risks (such as metabolic consequences) in adult life.

Consequences in Adulthood

There is a large body of evidence that suggests that low birth weight is associated with a wide range of metabolic and physiological disorders in later life (2). However, systematic reviews have suggested that the associations are small and that the possible impact on public health is uncertain (15, 72). The following discussion refers to risks in populations as opposed to individual risk. Most of the data are derived from cohorts not specifically restricted to SGA individuals.

Cardiovascular and metabolic consequences

Most of the evidence for the associations between birth weight and subsequent outcomes is derived from observational studies, so that there is potential for confounding. For example, poor socioeconomic position is associated with both lower birth weight and increased levels of cardiovascular risk factors in later life (*e.g.* obesity, BP, and smoking) (73, 74).

A modest positive association between birth weight and subsequent BMI and waist circumference has been reported (75). The typical effect size ranges from 0.6–0.7 kg/m^2 for each 1-kg increment in birth weight (75). In a systematic review, obesity risk has been reported to be related to rapid weight gain in infancy (12).

TABLE 1. GH use in short SGA children

	FDA-approved indication (2001)	EMEA-approved indication (2003)
Age at start (yr)	2	4
Height SDS at start	Not stated	−2.5 SD
Growth velocity before treatment	No catch-up	<0 SD for age
Reference to midparental height	Not stated	Height SDS > 1 SD below midparental height SDS
Dose (μg/kg·d)	70	35

EMEA, European Agency for the Evaluation of Medicinal Products; FDA, Food and Drug Administration.

An inverse association was also reported in many studies between birth weight and both BP and hypertension, but the overall effect size was 0.5 mm Hg lower systolic BP per 1-kg higher birth weight (72). There is little evidence that variation in preterm nutrition is associated with raised BP in later life (76).

For CHD, a 1-kg higher birth weight is associated with 10–20% lower incidence of CHD (Huxley, R., personal communication). However, potential residual confounders include maternal smoking and parental hypertension. A recent systematic review of cardiovascular disease has indicated that a 1-kg higher birth weight is associated with a 20% lower risk of CHD and stroke (77).

Both small and large size at birth has been reported to be associated with increased risk of type 2 diabetes and glucose intolerance (78).

Cancer

Low birth weight has not been shown to be associated with increased risk of cancer in general with the possible exceptions of testicular and to a lesser extent renal cancer (79, 80). By contrast, there is good evidence that high birth weight is associated with an increased risk of cancer, best documented for breast cancer (81, 82).

Intergenerational effects

Women (and possibly men) who were themselves SGA are reported to be at increased risk of having a SGA infant (83). Women born SGA are also at increased risk of preeclampsia and gestational diabetes (83).

Summary

Based on these population data, there is insufficient evidence to justify specific surveillance of adults born SGA. Screening procedures for cardiovascular risk factors, cancer, and osteoporosis should be in accordance with current clinical practice. Lifestyle interventions seem equally appropriate for this group as in the general population.

There are no long-term surveillance data on adults who have been treated with GH for short stature due to SGA. It is therefore prudent to follow up this group systematically.

Conclusions

The diagnosis of SGA should be based on accurate anthropometry at birth including weight, length, and head circumference. We recommend early surveillance in a growth clinic for those with lack of catch-up. Early intervention with GH for those with severe growth retardation should be considered. Long-term surveillance of all those who receive GH is essential. In view of the cognitive impairment reported in some children born SGA, early neurodevelopment evaluation and interventions are warranted in at-risk children.

Endocrine and metabolic disturbances in the SGA child are recognized, but there is no evidence to recommend routine investigation of all SGA children. We recognize significant gaps in knowledge with regard to the genesis of metabolic profile and outcome in SGA children. Research studies using genomic, proteomic, and/or metabolomic approaches are likely to identify risk factors related to fetal and postnatal growth that generate insulin resistance and associated complications.

The associations at a population level between low birth weight, including those born SGA, and CHD and stroke in later life are recognized, but there is inadequate evidence to recommend routine health surveillance of all adults born SGA outside of normal clinical practice.

Acknowledgments

Participants included the following: K. Albertsson-Wikland, Queen Silvia Children's Hospital, Gothenburg, Sweden; S. Arslanian, Children's Hospital, University of Pittsburgh, Pittsburgh, Pennsylvania; S. Blethen, Tercica, Brisbane, California; W. Blum, Eli Lilly & Co., Bad Homburg, Germany; J.-C. Carel, Faculte Cochin-Universite Paris V, Paris, France; P. Chatelain, Hopital Debrousse, Lyon, France; S. Chernausek, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; F. Chiarelli, University of Chieti, Chieti, Italy; J. Christiansen, Aarhus University Hospital, Aarhus, Denmark; P. Cohen, Mattel Children's Hospital at UCLA, Los Angeles, California; C. Cowell, Children's Hospital Westmead, Sydney, Australia; R. Crabbe, Serono, Geneva, Switzerland; K. Cruickshank, University of Manchester, Manchester, United Kingdom; W. Cutfield, University of Auckland, Auckland, New Zealand; J. Dahlgren, Queen Silvia Children's Hospital, Gothenburg, Sweden; F. de Zegher, University of Leuven, Leuven, Belgium; D. Dunger, University of Cambridge, Cambridge, United Kingdom; J. Gardosi, West Midlands Perinatal Institute, Birmingham, United Kingdom; A. T. Gibson, Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom; P. Ghirri, Universita degli Studi, Ospedale S. Chiara, Pisa, Italy; B. Gronning, Ferring, Copenhagen, Denmark; A. Hokken-Koelega, Sophia Children's Hospital/Erasmus MC, Rotterdam, The Netherlands; I. R. Holzman, Mount Sinai School of Medicine, New York, New York; R. Huxley, The George Institute, University of Sydney, Sydney, Australia.; L. Ibanez, University of Barcelona, Hospital Sant Joan de Déu, Barcelona, Spain; P. Lee, Pennsylvania State University College of Medicine, Hershey, Pennsylvania; C. Levy-Marchal, Robert Debre Hospital, Paris, France; B. Lippe, Genentech Inc., San Francisco, California; R. Malina, Tarleton State University, Stephenville, Texas; V. Mericq, University of Chile, Santiago, Chile; V. Rakov, NovoNordisk, Copenhagen, Denmark; P. Saenger, The University Hospital for the Albert Einstein College of Medicine, New York, New York; G. Saggese, University of Pisa, Pisa, Italy; R. A. Simmons, University of Pennsylvania and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; A. Singhal, Institute of Child Health, London, United Kingdom; T. Tanaka, National Centre for Child Health & Development, Tokyo, Japan; T. Tuvemo, Uppsala University, Uppsala, Sweden; J. M. Wit, Leiden University Medical Centre, Leiden, The Netherlands; and H. Wollmann, Pfizer GmbH, Tuebingen, Germany.

Received September 13, 2006. Accepted December 26, 2006.

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This work was written on behalf of The European Society of Paediatric Endocrinology, The Growth Hormone Research Society, The Lawson Wilkins Pediatric Endocrine Society, Sociedad Latino-Americana de Endocrinologia Pediatrica, The Asia Pacific Paediatric Endocrine Society, The Australasian Paediatric Endocrine Group, and The Japanese Society for Pediatric Endocrinology.

Disclosure Statement: P.E.C. has consulting arrangements with Tercica and receives lecture fees from Pfizer, Serono, and Novo Nordisk; S.C. has nothing to declare; P.C. has consulting arrangements with Pfizer, Novo Nordisk, and Ipsen and receives lecture fees from Pfizer, Novo Nordisk, Ipsen, and Ferring; G.J. has consulting arrangements with Pfizer and Novo Nordisk and receives lecture fees from Pfizer, Lilly, and Novo Nordisk; R.R. has consulting arrangements with Serono, Pfizer, and Lilly and receives lecture fees from Lilly and Pfizer; A.R. has consulting arrangements with Genentech, Pfizer, Novo Nordisk,

Insmed, and Tercica and receives lecture fees from Novo Nordisk, Genentech, and Pfizer; A.R. also has equity ownership in Insmed, Inc.

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