The 43rd International Symposium on Endocrinology and Metabolism was held 20–21 May, 2011, in Rome, Italy. One of the key sessions was the KIGS (Pfizer International Growth Database) highlights. Chaired by Professors Anita Hokken-Koelega (The Netherlands) and Margaret Boguszewski (Brazil), the session featured expert presentations that addressed two main topics of interest:

How do we understand and interpret results and analyses of epidemiological studies using registry data, in particular, morbidity and mortality data, in a growth hormone-treated population?

How does KIGS contribute to clinical practice, in particular, via observational studies and the KIGS Quality Insight Report?

The 2011 highlights session also marked the 24th anniversary of the founding of KIGS.

We hope you enjoy this summary.
How do randomized controlled trials and surveillance/registry studies differ? Plus, what are some of the basic methods used in epidemiologic studies to analyze data, and how should we evaluate their findings?

Joseph F. Heissler, PharmD, BCPS

Basic differences exist between randomized controlled trials (RCTs) and observational studies/surveillance registries. RCTs, for example, are primarily powered to meet efficacy endpoints (with safety usually a secondary endpoint), use strict inclusion/exclusion criteria to identify and study a selected homogenous population, and have limited duration of follow-up. As a result, they are not sufficient to detect adverse drug reactions or adverse events (AEs) that are rare or have a long latency period.

RCTs are considered the gold standard in evidence-based medicine. They are a fundamental component when submitting data for regulatory agency approval to market a new drug. Nevertheless, pharmacoepidemiological registries and surveillance databases—such as KIGS—provide important complementary information. Because they are based on patient management in large cohorts of patients followed in daily clinical practice, such registries and databases are a valuable tool to monitor long-term effectiveness and safety. They are also well-suited to capture rare AEs and reactions and those with a long latency. For this reason, complete reporting from KIGS participants is critical.

Epidemiology Studies

Epidemiology can be broadly categorized as either descriptive or etiologic. Descriptive epidemiology usually explores variation in disease occurrence; i.e., does a disease usually occur at certain times (e.g., a season, year, or decade), in certain places (e.g., a country or a region), in certain populations (e.g., young or old, male or female), or in certain occupations? Etiologic epidemiology explores disease causation, in particular, whether an “exposure” (e.g., to certain risk factors or medical intervention) increases or decreases the risk of developing a disease or has an impact on patient phenotype, disease progression, or any other pharmacoepidemiological parameter. Etiologic epidemiology uses either an experimental or nonexperimental/noninterventional methodology. In the former, subjects are randomly assigned either to receive an exposure or not; in the latter, as in KIGS, all subjects are exposed and findings are observational. In KIGS, exposure refers to Genotropin® (somatropin [rDNA origin] for injection) treatment. Medical history, diagnosis, concomitant medications, treatments, etc. are collected in Case Report Forms and included in the KIGS database. These factors can be examined as potential risk factors when querying the database with a specific research question.

Several criteria are used to explore the possibility of a causal nature of an association, including coherence with existing information (biological plausibility), consistency of the association, appropriateness of the time sequence, and specificity and strength of the association.1 Quantitative strength, the dose-response relationship, and study design are factors that increase probability of a true association.
The pharmaceutical industry is increasingly using observational methods to understand the safety profile of medications after they are approved and marketed. Relevant examples are postapproval descriptive epidemiology studies, which are carried out to describe the characteristics of the users of a new medicine and the patterns of its use and to measure a drug’s effectiveness at the population level. These are large studies that can detect small differences in the risk of common AEs, estimate the risk of rare events, and distinguish between background risk factors and effects of a particular medicine. In contrast to preapproval studies, postapproval studies provide safety data from populations that actually use a drug in “real-world” clinical practice settings.

There are several ways to measure disease occurrence in postapproval epidemiological studies, including the standardized incidence ratio (SIR). The SIR is calculated as the observed number of cases divided by the expected number of cases, where the observed number of cases equals the number of cases in exposed patients and the expected number of cases equals the number of cases to be expected in exposed patients if they had the same incidence rates as a reference population, e.g., unexposed patients.

**A Recent KIGS Epidemiology Study**

Using the KIGS database, Wilton et al. assessed cancer occurrence in patients treated with recombinant human growth hormone (GH) who had no known increased risk of developing cancer before starting GH replacement therapy. The incidence of cancer in this patient cohort was compared with the incidence in the general population using the SIR (i.e., relating the observed to expected number of cases with stratification for age, sex, and country). The study found no difference in the incidence rates of cancer overall (combined all types of cancers) between KIGS patients and the general population.

![KIGS logo](https://example.com/kigs.png)

**Fig.** A recent data analysis from KIGS, showing that GH treatment is not associated with an increase in cancer in GH-treated children. Reprinted from Wilton et al., © 2010 with permission from Elsevier.
In a total of 58,603 KIGS patients, 32 new malignant neoplasms were reported. Because the expected incidence rate was 25.3 (based on an incidence of 16.4 per 100,000 patient-years), there was no statistical difference between exposed and unexposed subjects in rates of all cancers. There was a significant difference in the incidence rate of brain cancer.

The study showed an increased SIR of 1.26, but this should be interpreted with caution. Even though an epidemiology registry can control for factors such as GH replacement and stratify by age, sex, and country, it cannot control for numerous potential biases and confounders stemming from selection of a general population for comparison. Such factors may contribute to an increased SIR. In addition, when a study performs numerous comparisons, “play of chance” alone can produce statistically significant differences that may not be clinically significant.
How KIGS Contributes to Observational Studies

Jovanna Dahlgren, MD, PhD

Professor Dahlgren began by highlighting the complementary nature of RCTs, which study homogenous populations and, on the other hand, observational databases, which reflect the heterogeneity of daily clinical practice, and then summarized the strengths and weaknesses of each.

The advantages of RCTs include use of control groups, adjustments for secular changes, diminished selection bias, and accurate, comprehensive data collection, while observational studies are strengthened by their grounding in conditions of routine clinical practice, inclusion of a wide variety of patients, and long-term follow-up, which can allow patients to be divided into subgroups for further analysis. Limitations of RCTs include strictly defined treatment conditions, short length of follow-up, and selected populations. In addition, RCT populations are often too small for subgroup analysis. RCTs have strict inclusion and exclusion criteria, and in some studies this may lead to loss of information. For example, a recent RCT of a swine influenza vaccine excluded children. Postapproval surveillance showed increased rates of certain AEs, such as narcolepsy, in this group. As a result, the US Food and Drug Administration and the European Medicines Agency now require the inclusion of children in vaccination studies. Limitations of observational studies based on voluntary databases include lack of a control group, selection bias, less-than-complete data collection, and unequal follow-up.

The Pfizer Endocrine Care Databases and Publications

KIGS, initiated in 1987, is the oldest of the three Pfizer Endocrine Care databases. As of December 2010, KIGS has data on >76,000 patients from 51 countries who received Genotropin® during childhood. KIMS—the Pfizer International Metabolic Database—was started in 1994 and as of December 2010 contains data on >15,000 patients from 31 countries who are receiving GH replacement for adult GH deficiency. ACROSTUDY has been collecting data since 2004 on patients with acromegaly who are being treated with Somavert® (pegvisomant), and it includes >1,500 patients to date. All have made substantial contributions to the medical literature.
Recently published studies from the KIGS database include analyses of predicted responses to GH treatment in prepubertal children with growth disorders\textsuperscript{3} and chronic kidney disease\textsuperscript{4} and the first-year outcome of GH treatment in preterm children.\textsuperscript{5} In a 2009 KIGS efficacy analysis, Ranke et al showed that age, GH dose, and midparental height predict first year growth during GH replacement therapy.\textsuperscript{6}

Databases are also of great value in analyzing safety. For example, Darendeliler et al reported that KIGS patients with Turner syndrome, organic GH deficiency, Prader-Willi syndrome, and chronic renal insufficiency seem to be more prone to idiopathic intracranial hypertension and slipped capital femoral epiphysis than patients in other diagnostic groups.\textsuperscript{7} Impairment of quality of life (QoL) is a key clinical characteristic in adult GH deficiency and it has been extensively studied in KIMS. In adolescents as well as adults, KIMS has shown improvement in QoL, especially in energy-related dimensions, during GH replacement.\textsuperscript{8} In addition to publications, other KIGS programs and activities include:

*The KIGS Growth Prediction System (GPS)—which uses KIGS data and prediction models for the individual patient.*
Fig. The KIGS growth prediction system (GPS) has proved to be very useful in providing robust height predictions that can be used in clinical management.

The KIGS Quality Insight Report—which allows an individual center to compare outcomes with country-wide data. [Note: this program is described in the following article.]

The Rare Diseases Section of the KIGS home page (http://www.medicaloutcomes.pfizer.com) — which presents information on children with rare diseases who are receiving GH treatment.

KIGS, KIMS, and ACROSTUDY contribute to optimization of clinical outcomes, by individualizing treatment, predicting treatment response, and improving cost-effectiveness.
How KIGS Contributes to Clinical Practice: Experience in Germany with the KIGS Quality Insight Report
Helmuth G. Dörr, MD

The KIGS Quality Insight Report is an ongoing pilot project that was begun in 2007 in Germany. It has three goals: to give information back to physicians participating in KIGS, to further develop the relation between KIGS and participating physicians, and to improve quality of care.

In essence, a KIGS Quality Insight Report allows physicians to compare their treatment data with treatment data on a national scale. It enables clinicians to see how effectively they treat their patients compared with other centers in their country. In developing the KIGS Quality Insight Report, the following prerequisites were paramount: only existing data sets were to be evaluated; no additional time and effort would be required from participating physicians; and relevant, patient-specific data, with patient and center confidentiality maintained, would be generated.

The KIGS Quality Insight Report template can be customized to each country and to each clinician’s needs. Countries that have few centers prescribing GH treatment can request pooled data from a nearby country with a larger number of centers for comparison.

Each Quality Insight Report begins with a brief overview/summary and then provides a wealth of data on such areas as demographics, diagnosis, characteristics at treatment start, completeness of documentation, auxology, and status. Centers with < 10 patients will receive a report showing data for each individual patient; centers with ≥ 10 patients will receive median values for each patient group. Professor Dörr then presented a sample Quality Insight Report.
Fig. A sample KIGS Quality Initiative Report, in which the participating center receives information on how it compares with the country as a whole on such parameters as numbers of active and nonactive patients, indications, patient characteristics at initiation of therapy, mean GH doses (µg/kg/day) based on indications, completeness of documentation, and growth patterns.

The report also contains an index of responsiveness (IoR), a measure of a patient’s ability to respond to therapy after first year on GH treatment. IoR values outside the 10th and 90th percentiles can be used to identify patients who are not responding as well as expected. Data on AEs are also provided to allow a center to see how its rates of AEs compare with those of the entire country.

In summary, the KIGS Quality Insight Report is a notable effort to improve patient care, share best practices, and enable demonstration of treatment standards on a country-by-country basis.
References:


