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Assessment of Primary Cancer Incidence in Growth Hormone-Treated Children: Comparison of a Multinational Prospective Observational Study with Population Databases

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Key Words
Growth hormone · Primary cancer · Paediatrics · Standardised incidence ratio

Abstract
Background/Aims: Although results of the majority of clinical studies have shown no association between growth hormone (GH) treatment in childhood and risk of primary cancer, concerns remain regarding the potential influence of GH therapy on neoplastic cell growth. This study evaluated the incidence of primary malignancies in a large observational study of paediatric GH treatment. ***Methods:*** Primary cancer incidence was assessed in a cohort of 19,054 GH-treated children without a reported prestudy history of malignancy in the observational Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS). The standardised incidence ratio (SIR) for primary cancer in GH-treated children was determined by comparing cancer incidence in the GeNeSIS study population with incidence rates for country-, age-, and sex-matched cohorts of the general population. ***Results:*** During a mean follow-up of 3.4 years in GeNeSIS (64,705 person-years), 13 incident potential primary cancers were identified in GH-treated patients. The SIR (95% confidence interval) for all observed cancers was 1.02 (0.54–1.75), and the crude incidence was 20.1 (10.7–34.4) cases per 100,000 person-years. ***Conclusion:*** Acknowledging the relatively short follow-up in our study, GH-treated children without a history of previous malignancy did not have a higher risk of all-site primary cancer during the study when compared to general-population cancer registries.

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Introduction

Childhood growth hormone (GH) treatment has been approved for a number of conditions that result in short stature. After initial approval in 1987 for children with significant GH deficiency (GHD), GH therapy has been approved, after demonstration of its efficacy and short-term safety, in various countries and for various manufacturers for treatment of short stature or growth failure associated with Turner syndrome (TS), short stature homeobox-containing *(SHOX)* gene deficiency, Prader-Willi syndrome, and chronic renal insufficiency and in children born small for gestational age (SGA) who do not demonstrate catch-up growth. In the USA and certain

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other countries, but not in the European Union, GH therapy is also approved for idiopathic short stature (ISS) and for treatment of short stature associated with the Noonan syndrome [1].

Since the late 1980s, there has been considerable discussion regarding the potential influence of GH therapy on neoplasia due to the general growth-inducing effects of GH. Such concerns were especially prompted when leukaemia in GH-deficient children receiving GH replacement therapy was first reported [2], although most of the reported cases had concomitant conditions predisposing them to cancer. Reassuringly, multiple studies have found the rates of leukaemia in GH-treated patients without leukaemia risk factors to be similar to those of the general population [3–6]. Additionally, concerns have been raised about the possibility of an association between GH treatment and occurrence of neoplasms, because in vitro and animal studies have indicated that GH and insulin-like growth factor 1 (IGF-1) can be mitogenic [7–9]. Likewise, epidemiological studies have indicated a positive correlation between serum IGF-1 concentration and risk of certain malignancies typically observed in adulthood [10–12].

The majority of studies that evaluated the risk of de novo neoplasms in patients without previous malignancy who received childhood treatment with either cadaveric or recombinant GH detected no increase in rates of de novo neoplasms either during treatment or in post-treatment follow-up [3–6, 13]. However, in 2002, Swerdlow et al. [14] reported a statistically significantly elevated standardised incidence ratio (SIR) of colorectal cancer, albeit based on 2 cases, in their cohort of 1,848 patients previously treated with cadaveric GH. Although there were only 2 cases and differences in treatment regimens between previous human cadaveric and recombinant GH treatments, the results supported a continued need for the surveillance of GH-treated patients for the development of de novo malignancies. Subsequently, results from 2 large observational study programmes have shown that the rates of new malignancies in patients without risk factors were not significantly higher than the cancer rates expected from the general population [5, 6].

The majority of studies in survivors of previous neoplasia, particularly brain tumours, have not indicated an association between GH treatment and increased tumour recurrence or occurrence of second neoplasms [5, 6, 15]. Early reports from the Childhood Cancer Survivor Study (CCSS) indicated that GH treatment was associated with a higher relative risk of second neoplasms [16, 17] – findings supported by an earlier analysis from the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) [18]. However, a recent CCSS follow-up report with an extended length of surveillance did not show a significantly higher risk of secondary central nervous system tumours among long-term survivors who had received GH treatment during childhood [19]. Although GH treatment was not associated with a higher risk of mortality in the CCSS [16], data from the French cohort of the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) study showed a higher risk of mortality in adulthood in a group of patients who were treated with GH during childhood for isolated idiopathic GHD, ISS, or being born SGA [20]. Bone tumour-related, cerebrovascular disease-related, and overall mortality rates were higher than those for the French general population.

Investigation of primary cancer rates among patients who receive paediatric GH treatment, whatever the indication, remains important. The observational GeNeSIS programme has been ongoing since 1999 to examine the safety and effectiveness of GH treatment in children with short stature resulting from various aetiologies. The present analysis aimed to assess primary incidence rates for GH-treated paediatric patients followed in GeNeSIS and to determine the SIR by comparing cancer incidence in the study population with incidence rates from the general population.

Subjects and Methods

Study Design and Overall Study Population

GeNeSIS is an open-label, multinational observational study (ClinicalTrials.gov, NCT01088412) sponsored by Eli Lilly and Company (Indianapolis, Ind., USA). The study collects information on clinical management and treatment outcomes of patients with growth disorders as documented by the attending clinician during standard endocrine practice. Designed in a modular fashion, the global GeNeSIS programme includes a 'core study' in which all patients are enrolled that addresses the primary objectives of the safety and effectiveness of somatropin treatment. Optional substudies for specific patient subgroups include the Neoplasia Sub-Study, which collects additional details on neoplastic diagnoses and disease course. Paediatric patients who were receiving or starting Humatrope® (GH, somatropin; Eli Lilly and Company) for treatment of a growth disorder or hypothalamic-pituitary dysfunction were enrolled in GeNeSIS. Non-GH-treated patients, including those with a history of neoplastic disease, are also followed in GeNeSIS for a subset of growth disorders. However, because of the small sample size relative to treated patients, these non-GH-treated patients were not included in the analysis for this report. Patients were considered in the GH-treated group if they had received GH therapy before the beginning of the study and/or if they received at least one GH dose during study.

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The GeNeSIS programme is conducted in accordance with the guidelines in the Declaration of Helsinki. Institutional review board approval was obtained, and all applicable regulatory requirements in the participating countries were followed. Patients' parents (or guardians) provided written consent for data collection, electronic processing, and publication in accordance with national requirements. The study protocol requires that investigators report all adverse events in participating patients, irrespective of whether a causal relationship with GH treatment is suspected.

At the time point of these analyses (including patient data from March 1999 to September 2013), GeNeSIS enrolment had reached 20,060 GH-treated patients with at least one follow-up visit available from approximately 800 sites in 30 countries.

Cancer History and Incident Case Ascertainment

Study data, including short stature diagnoses, historical diagnoses, pre-existing conditions, adverse events, and Neoplasia Sub-Study diagnoses, were used to identify those with reported previous malignancy. Where applicable, historical details were cross-checked with information from serious adverse event (SAE) reports in the corporate pharmacovigilance system. Malignancy status was based on the Surveillance, Epidemiology, and End Results (SEER) guidelines [21] and World Health Organisation (WHO) classification [22]. Patients with a pre-enrolment history of cancer were excluded from the analysis. The same data sources used to determine cancer history were used to ascertain incident cancer cases. Only de novo primary cancers in patients with no history of neoplastic disease or cancers in patients with previous benign neoplasia were included as incident cases for these analyses. Although only incident cancer cases with onset after the date of enrolment in GeNeSIS were meant to be included in this analysis, one additional case that occurred after the recorded start of GH but before GeNeSIS entry was ascertained from the Neoplasia Sub-Study and was included in the case count.

In some instances the status of a historical event as a malignancy or resulting from a malignancy could not be clearly determined; for instance a potentially but not definitively cancer-related intervention (e.g. bone marrow transplant) had been performed, or the malignancy status could not be determined from any of the available information. In all such cases, the patients were excluded from the analyses on the basis of unknown malignancy status. There were no incident cases of subsequent cancers in the patients with unknown malignancy status. In taking data from a variety of sources within the GeNeSIS database, if the history or case was reported in multiple modules, the most descriptive detail was used to define the history or case. Where more than one pathology or type of neoplasm was reported, the most malignant and/or invasive pathology was used to define the patient's history or incident disease. In this paediatric patient population, determining malignancy status for astroglial tumours was the most problematic. Historical astrocytomas stated to be pilocytic, grade 1, or low grade and gliomas defined as optic nerve gliomas were not considered malignant, and thus patients with histories of these tumours were included in the analysis population at risk of primary cancer. On the other hand, historical astrocytomas and gliomas of unspecified grade were considered malignant, and thus affected patients were excluded from the analysis population. There were no incident cases of second cancers among the patients with astrocytoma and glioma of unspecified grade and/or location.

Table 1. Summary of patient demographics and GH treatment for GH-treated patients without a recorded history of malignancy

Parameter	GH-treated patients without previous malignancy
Patients, n	19,054
Female/male, %	40/60
Naïve to GH at study entry/previously treated, %	67/32
Age at the start of GH treatment, years	9.5±4.0
Age at study entry, years	10.4±3.8
Median (Q1–Q3) GH dose at study entry, mg/kg/week	0.26 (0.20–0.32)
Time on study, years	3.4±2.5
Total person-years of follow-up during study	64,705
Time from start of GH therapy, years	4.2±3.1

Values are expressed as means ± SD unless specified otherwise. Q1 = 1st quartile; Q3 = 3rd quartile.

Statistics

The study was planned to accrue 60,000 person-years in order to provide 90% power to rule out an SIR relative to the general population of 2.5 and 70% power to rule out an SIR of 2, both at a 95% confidence level. SIRs and associated 95% confidence intervals (CIs) for all-site primary cancer were determined by country as the ratio between the number of cases observed in GeNeSIS and the expected number of incident cases based on country-, gender-, race-, age-, and calendar year-specific cancer incidence rates for the US general population from the SEER programme [21], or country, gender-, and age-specific cancer incidence rates for the general population from GLOBOCAN for all other countries [23]. Country-specific SIRs were calculated from the sum of the strata and an overall SIR from an aggregate of the country-specific data. The observed number of cancer cases was assumed to follow a Poisson distribution, and 95% CIs were calculated using an exact method [24]. Given the limited number of cancer cases expected among paediatric patients with no previous cancer history, SIRs for specific cancer types or groups were not calculated.

The follow-up time per patient was calculated from the date of visit 1 – or the date of the first GH dose in GeNeSIS if this was later – until the date of the last contact, last available follow-up visit, study completion date, cancer onset date, or date of death, whichever was the latest occurrence.

Results

Cohort of Patients without a Reported History of Malignancy

A cohort of 19,054 patients without a recorded history of malignancy was identified (online suppl. table S1 indicates the numbers of patients in this cohort split by par-

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Table 2. SIRs for primary cancers (all sites), by country and overall, in GH-treated patients

Country[1]	Patients, n	Person-years of follow-up	Observed cancer cases, n	Expected cancer cases, n	SIR (95% CI)
Canada	656	2,758	3	0.76	3.94 (0.81–11.52)
France	1,439	5,424	2	1.32	1.52 (0.18–5.49)
Germany	2,507	12,270	5	3.15	1.59 (0.52–3.71)
Japan	2,051	5,973	1	0.78	1.29 (0.03–7.18)
USA[2]	8,465	24,660	2	3.83	0.52 (0.06–1.89)
Overall[2]	19,054	64,705	13	12.71	1.02 (0.54–1.75)

[1] Countries with no incident cases are not listed in the table, but the follow-up time is included in the overall SIR calculation (Australia, Austria, Belgium, Czech Republic, Denmark, Finland, Greece, Hungary, Iceland, India, Italy, Kazakhstan, Lithuania, Norway, Pakistan, Russia, Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan, Thailand, The Netherlands, and UK). [2] Using SEER (1992–2011) data for the USA; for all other countries, GLOBOCAN 2012 was used.

ticipating country; for all online suppl. material, see www.karger.com/doi/10.1159/000444124). Of this cohort, 40% were girls and 60% boys, and diagnoses associated with short stature were as follows: GHD, 63%; ISS, 13%; TS, 9%; SGA, 6%, and other diagnoses (including *SHOX* gene deficiency, genetic defects, and clinical syndromes), 9%. The patients' demographics and parameters associated with GH treatment are summarised in table 1; the mean follow-up ± standard deviation per patient during GeNeSIS was 3.4 ± 2.5 years, with the total person-years of follow-up equalling 64,705. The mean age at the beginning of GH treatment was 9.5 ± 4.0 years, with the age at study entry being approximately 1 year more (at 10.4 ± 3.8 years), reflecting pretreatment with GH before study entry for approximately one third of the patients (table 1).

Cancer Cases and Comparison of Incidence Rates with General Population Reference Data

A total of 13 incident potential cancers were reported from 5 of the 30 participating countries (table 2). Expected cancer cases for all countries combined were estimated at 12.71, giving an overall SIR (95% CI) for all-site primary cancers of 1.02 (0.54–1.75). Although certain countries had elevated estimated SIRs, no country-specific SIR was statistically significantly elevated, and the numbers of expected and observed cases were low. The crude incidence of all-site primary cancers in GeNeSIS was 20.1 (10.7–34.4) cases per 100,000 person-years.

The incident cancers were 4 lymphomas, 3 germ cell tumours, 2 bone tumours (Ewing's sarcoma and osteosarcoma), and 1 case each of neuroendocrine tumour, rectal cancer, malignant schwannoma, and skin cancer (table 3). No cases of leukaemia were reported. The reported lymphomas were: B-cell lymphoma in a boy with Russell-Silver syndrome; Burkitt's lymphoma with manifestation in the stomach, pancreas, and kidney in a girl with idiopathic GHD; Burkitt-like lymphoma in the thyroid gland of a girl with TS, and lymphoma of unspecified type (not reported as an SAE) in a 12-year-old boy with idiopathic GHD. Four of the 13 patients with tumours had previous neoplastic disease and/or a predisposition: a case of rectal adenocarcinoma in a patient with neurofibromatosis and Gardner syndrome; a pancreatic neuroendocrine tumour in a patient with neurofibromatosis; malignant schwannoma in a patient with previous WHO grade 1 astrocytoma and neurofibromatosis, and gonadoblastoma in the streak gonad of a 15-year-old girl with 46,XY mixed gonadal dysgenesis. The case of osteosarcoma in a 14-year-old boy was not reported as an adverse event, but as a Neoplasia Sub-Study diagnosis – pre-existing at study entry but treatment emergent to GH therapy (diagnosed 10 years after starting GH treatment). A case of Ewing's sarcoma was reported for a 16-year-old girl with TS and GHD. Approximately 9 years after the first GH dose and 3 years and 6 months after the last GH dose, she was diagnosed with pelvic Ewing's sarcoma with spinal metastases. Biopsy indicated pathology consistent with Ewing's sarcoma and positive translocation involving the *EWSR1* gene and the chromosome 22q12 location [25]. One intracranial germ cell tumour was reported with a likely differential diagnosis of non-germinomatous germ cell tumour (and thus included as a malignancy), but the case narrative also proposed an alternative diagnosis of craniopharyngioma (benign) because of the

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Table 3. Summary of reported cancer cases and relevant patient histories

Country	Short stature diagnosis	Age at reported cancer diagnosis, years	GH start to cancer diagnosis, years	GH status at cancer diagnosis[1]	Sex	Cancer type	Relevant history/other factors
Canada	TS	16.9	9.0	Off (3.6 years)	F	Ewing's sarcoma (pelvic/spinal metastases)[2]	Tumour pathology positive for translocation involving the *EWSR1* gene and the chromosome 22q12 location
Canada	Acquired GHD	15.4	3.8	Ongoing	M	Pancreatic neuroendocrine tumour	History of hamartomas and neurofibromatosis; tumour reported as having 'possible malignant behaviour'
Canada	Congenital GHD	14.4	~10	Unknown	M	Osteosarcoma	Reported to Neoplasia Sub-Study (after GH start/before GeNeSIS start); included, although outside of defined analysis period
France	Acquired GHD	16.0	3.0	Ongoing	M	Rectal cancer	Irradiation for recurrent neurofibromatosis, diagnosed with Gardner syndrome
France	ISS (CDGA)	15.6	0.9	Ongoing	F	Gonadoblastoma	Tumour reported as 'testicle with gonadoblastoma' in a girl with 46,XY mixed gonadal dysgenesis
Germany	SGA (RSS)	9.1	6.0	Ongoing	M	B-cell lymphoma	–
Germany	IGHD	16.1	10.2	Off (1.3 years)	F	Burkitt's lymphoma	–
Germany	IGHD	12.1	~8	Unknown	M	Lymphoma	–
Germany	TS	14.0	5.6	Ongoing	F	Burkitt-like lymphoma[3]	–
Germany	Acquired GHD	13.4	1.5	Ongoing	M	Malignant schwannoma	History of WHO grade 1 astrocytoma (surgery and chemotherapy) and neurofibromatosis
Japan	IGHD	8.2	5 weeks	Ongoing	F	Germinoma (around pituitary)	Diagnosis of hypophysitis prior to GH exposure with diabetes insipidus and hypothyroidism; tumour diagnosed upon routine MRI just 5 weeks after GH therapy initiation
USA	Acquired GHD	12.4	3.8	Ongoing	M	Germ cell tumour[4]	Considered possibly a craniopharyngioma (benign) because of the cystic structure; short stature diagnosis given as 'unknown acquired cause', with GHD and diabetes insipidus in the history
USA	ISS	12.2	0.7	Ongoing	M	Skin cancer (malignant naevi)	–

CDGA = Constitutional delay of growth and adolescence; IGHD = idiopathic GHD; RSS = Russell-Silver syndrome. [1] Indicates whether GH treatment was ongoing up until the onset and/or diagnosis of the cancer, with 'time since GH treatment was stopped (for other reasons)' in parentheses. [2] Fatal during GeNeSIS participation. [3] Unresolved differential diagnosis between Burkitt's lymphoma and diffuse large-cell B-cell lymphoma. [4] Reported with a likely differential diagnosis of non-germinomatous germ cell tumour.

highly cystic nature of the lesion. A Japanese patient with a diagnosis of hypophysitis before GH exposure was diagnosed with germinoma around the pituitary gland upon routine magnetic resonance imaging (MRI) 5 weeks after initiation of GH therapy.

The mean age ± SD at the reported onset of cancer was 13.5 ± 2.7 years, while the time from the beginning of GH therapy to the onset of cancer ranged from 5 weeks to approximately 10 years. Three of the 13 incident potential malignancies were reported to have occurred within 1

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year of the initiation of GH therapy (table 3); 62% occurred in patients naïve to GH at study entry, and 38% in patients who had previously been treated before study entry.

Discussion

The projected sample size requirement for the GeNeSIS core study was based on primary safety-related objectives that included determining the incidence of de novo cancer in GH-treated children without a history of neoplastic disease. Because of the mode of action of GH and the reported high rates of specific cancer types in certain study populations, concerns have remained that GH treatment may be associated with higher cancer risk. In comparison with general population cancer registries there appeared to be no higher risk of all-site primary cancers in GH-treated patients in GeNeSIS who were without a history of malignancy. Unsurprisingly, in this cohort there is a low number of expected and observed cases; therefore, interpretation of the results is somewhat difficult. The overall SIR of 1.02 for all countries combined has a reasonably tight 95% CI, whereas the SIRs for individual countries had much wider confidence limits, and all included unity (a value of 1.0, indicating 'not statistically significant'). These findings are generally similar to those from analyses of other observational studies of GH treatment. Results from both the KIGS and NCGS databases indicated no higher risk of all-site primary cancers among patients with no risk factors for malignancy than for the general population [5, 6, 26]. The estimated crude incidence rate in GeNeSIS of 20.1 cases per 100,000 person-years was similar but higher than that in KIGS at 16.4 cases per 100,000 person-years [6]. In our analyses, patients with risk factors for cancer development were included as long as they had not had previous cancer. Therefore the genotype/phenotype of such patients must be taken into account, and the patients have to be closely monitored for neoplastic disease during GH treatment.

The most prevalent type of incident primary cancer observed in GeNeSIS was lymphoma. All lymphoma cases were reported in German patients, but no risk or other mitigating factors could be identified from study or SAE reports. In an analysis of the KIGS database, 4 incident cases of lymphoma (3 non-Hodgkin lymphomas and 1 Hodgkin lymphoma) were observed during the follow-up of 58,603 patients without a history of cancer or other medical conditions known to increase cancer risk, such as neurofibromatosis [6]. Similarly, 4 cases of incident lymphomas were reported in an analysis of approximately 50,000 patients without previous malignancy enrolled in the NCGS [5]. Thus, the rate of observed lymphoma in our smaller cohort appears higher than that in the previously published analyses.

The 3 reported cases of potential germ cell tumours had a pre-existing risk or other mitigating factors. The first was a gonadoblastoma reported in the streak gonad of a girl with 46,XY mixed gonadal dysgenesis. The streak gonads typical of 46,XY phenotypic females are reported to have a 30% risk of development of gonadoblastoma, which, although in itself considered benign, carries a significant risk of malignant transformation, most commonly to dysgerminoma [27]. The second case, reported most likely to be a non-germinomatous germ cell tumour, had a suggested alternative pathology of craniopharyngioma – which would, by definition, be excluded from our analyses. The third case, a pituitary germinoma, was identified 5 weeks after initiation of somatropin therapy; previous MRI had indicated hypophysitis, and cases of hypophysitis preceding or masking a diagnosis of germinoma have previously been described [28]. This fact, coupled with the short time between the start of GH treatment and diagnosis of the tumour, suggests that the germinoma may have been present before initiation of GH therapy.

An analysis of the French SAGhE cohort showed that although all-type cancer-related mortality was not higher, bone tumour-related mortality was found to be significantly increased [standardised mortality ratio 5.00 (95% CI 1.01–14.63)] in young adults previously treated with GH as children when compared to French general population data [20]. Despite the small number of cases (2 osteosarcomas and 1 Ewing's sarcoma), it was concluded that such an effect was biologically plausible on the basis of the rapid phase of growth, relationship to the accrued height [29], and potential associations with the IGF-1 system [7, 30]. Two bone cancers were identified in our analysis of the GeNeSIS database, both in patients from Canada. The patient with Ewing's sarcoma was positive for translocation involving the *EWSR1* gene and the chromosome 22q12 location [25]. The other bone tumour, an osteosarcoma, was pre-existing at study entry but appeared treatment emergent to GH therapy. Although by definition outside the date range for inclusion in the calculation of follow-up during study, this case was included to maintain a conservative analysis. It should be noted that our data are not directly comparable to the French SAGhE study because of differences in study design (follow-up during GH treatment in GeNeSIS vs.

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post-treatment in SAGhE) and duration of follow-up (much longer in SAGhE).

The remaining 4 tumours of the total of 13 were individual cases of different tumour types; 3 of the affected patients had previous neoplastic disease and/or a predisposition to tumour development. One case of colorectal cancer was reported, but the patient had a noteworthy history of Gardner syndrome (familial polyposis coli or familial adenomatous polyposis) [31] and irradiation for recurrent neurofibromatosis. An association has been suggested between high serum IGF-1 concentrations and breast, prostate, and colorectal cancers in adults [7]. A higher risk of colorectal cancer [SIR 7.9 (95% CI 1.0–28.7)] was reported, albeit based on only 2 observed cases, in a UK-specific cohort study that followed up on adults previously treated with pituitary-derived GH during childhood or early adulthood [14]. A neuroendocrine tumour, described by the investigators as having 'possible malignant behaviour', was reported in a patient with history of hamartomas and neurofibromatosis, and malignant schwannoma in a patient with a history of surgery and chemotherapy for astrocytoma (WHO grade 1). The final case was a report of 'naevus formation, malignant' (a likely melanoma) in a 12-year-old boy with ISS. Skin cancer in a 12-year-old boy without previous neoplastic disease and/or irradiation appears an unexpected finding. Additional information was unavailable, because no medical history had been reported for this patient, and the case was not reported as an SAE. Only limited case reports of melanoma in association with GH exposure are available in the literature, and these are reports from adults [32, 33]. No cases of de novo leukaemia were observed in the GeNeSIS cohort of patients without previous malignancy.

Although the results showing no difference in all-site primary cancers between patients enrolled in GeNeSIS and the general population are comforting and are in agreement with previous studies [34], there are a number of limitations to our analyses to consider. The average follow-up time per patient in GeNeSIS was relatively short (a mean of 3.4 years for all GH-treated patients). Because approximately one third of the patients had previously been treated with GH before entering the study, the average time from initiation of GH treatment to reported cancer onset was approaching 1 year more than the follow-up time within the study (mean 4.2 years). The analysis could have been based on the follow-up time since the beginning of GH treatment (adding approx. 15,000 more person-years), but because we cannot be certain that a cancer was diagnosed after GH initiation but before enrolment in GeNeSIS, only the time during GeNeSIS was used for calculating the SIR, creating a more conservative analysis. However, it is unlikely that any cases incident to GH therapy, but occurring before the start of the study, were miscategorised as historical in nature and thereby excluded from analysis. Ascertainment of patient assessments as having no reported prestudy malignancy was primarily based on review of the short stature diagnoses that led patients to be considered for GH therapy in the first place, and not the 'historical and pre-existing conditions' case report form fields that are based on a temporal association with GH exposure. Additionally, as GeNeSIS is an observational study, reporting of incident cases was dependent on the investigative site, in general without sponsor monitoring of patient medical records. While a potential underreporting of event cases in such studies must be considered, for these analyses, multiple data modules from the GeNeSIS and corporate pharmacovigilance databases were used to ascertain cases, and the sites were reminded of the importance of adverse event reporting throughout study participation. Similarly, it should be acknowledged that our comparison of GeNeSIS data is with general population cancer registries that may be subject to unknown biases and are from countries with a varied quality of health care systems.

Cancer/tumour induction time was not used to adjust our analyses. There is the possibility that a higher risk of neoplastic disease might be revealed with longer GH treatment and/or follow-up. However, it can also be argued that cases diagnosed soon after GH initiation in GeNeSIS were unlikely because of GH treatment, so inclusion of such cases may lead to overestimation of cases truly associated with GH exposure. Additionally, reports of cancer diagnosis are often based on pathological analysis (e.g. MRI or biopsy) and not necessarily on onset of cancer symptoms, with the potential effect of shortening the apparent period between onset of GH therapy and cancer diagnosis. Because follow-up time accrual was only that during GeNeSIS participation, no extra time would have been added to the person-year calculation for a patient treated with GH before study entry. Additionally, one case – the osteosarcoma – was reported as a diagnosis in the Neoplasia Sub-Study with onset before the patient's first GeNeSIS visit but after initiation of GH treatment. Although no person-years for the period before GeNeSIS participation were included in the calculation, the case was included as an incident case in this conservative analysis. Finally, the case histories did not always have enough detail to determine whether they were malignant; patients with histories of conditions of un-

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known malignancy status and those with interventions that potentially could have been but which were not definitively identified as related to cancer were not included in these analyses. Removal of these patients' data from the analyses lowered the person-years of GH exposure and thereby the number of expected cancer cases, but, crucially, no cases of incident primary cancer were observed among these patients. We believe that these factors, together with the fact that a significant proportion of the incident cases have significant risk factors and/or other mitigating circumstances, make this analysis conservative in nature.

In conclusion, in our analysis with a relatively short follow-up time during the study, GH-treated paediatric patients who had no history of previous malignancy did not appear to have a higher risk of all-site primary cancer during GeNeSIS when compared to general population cancer registries.

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Disclosure Statement

C.J. Child, A.G. Zimmermann, and N. Jia are employees and stockholders of Eli Lilly and Company (Indianapolis, Ind., USA). L.L. Robison and J.H. Brämswig have been members of Medical Research advisory boards for and have received consulting fees from Eli Lilly and Company. W.F. Blum is a former employee and stockholder of Eli Lilly and Company.

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