Predicting the Optimal Basal Insulin Infusion Pattern in Children and Adolescents on Insulin Pumps

Paul-Martin Holterhus, MD[1]
Jessica Bokelmann, MD[1]
Felix Riepe, MD[1]
Bettina Heidtmann, MD[2]
Verena Wagner, MD[3]
Birgit Rami-Merhar, MD[4]
Thomas Kapellen, MD[5]
Klemens Raile, MD[6]
Wulf Quester, MD[7]
Reinhard W. Holl, MD[8]
the German/Austrian DPV-Initiative and the German Pediatric CSII Working Group

OBJECTIVE—We aimed at developing and cross-validating a mathematical prediction model for an optimal basal insulin infusion pattern for children with type 1 diabetes on continuous subcutaneous insulin infusion therapy (CSII).

RESEARCH DESIGN AND METHODS—We used the German/Austrian DPV-Wiss database for quality control and scientific surveys in pediatric diabetology and retrieved all CSII patients <20 years of age (November 2009). A total of 1,248 individuals from our previous study were excluded (dataset 1), resulting in 6,063 CSII patients (dataset 2) (mean age 10.6 ± 4.3 years). Only the most recent basal insulin infusion rates (BRs) were considered. BR patterns were identified and corresponding patients sorted by unsupervised clustering. Logistic regression analysis was applied to calculate the probabilities for each BR pattern. Equations were based on both independent datasets separately, and probabilities for BR patterns were cross-validated using typical test patients.

RESULTS—Of the 6,063 children, 5,903 clustered in one of four major circadian BR patterns, confirming our previous study. The oldest age-group (mean age 12.8 years) was represented by 2,490 patients (42.18%) with a biphasic dawn-dusk pattern (BC). A broad single insulin maximum at 9–10 P.M. (F) was unveiled by 853 patients (14.45%) (mean age 6.3 years). Logistic regression analysis revealed that age, to a lesser extent duration of diabetes, and partly sex predicted BR patterns. Cross-validation revealed almost identical probabilities for BR patterns BC and F in the two datasets but some variation in the remaining two BR patterns.

CONCLUSIONS—Reconfirmation of four key BR patterns in two very large independent cohorts supports that these patterns are realistic approximations of the circadian distribution of insulin needs in children with type 1 diabetes. Prediction of an optimal pattern a priori can improve initiation and clinical follow-up of CSII in children and adolescents. In addition, these BR patterns represent valuable information for insulin-infusion algorithms in closed-loop CSII.

From the [1]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, Christian-Albrechts-University of Kiel, University Hospital of Schleswig-Holstein, Campus Kiel, Kiel, Germany; the [2]Division of Pediatric Endocrinology and Diabetes, Catholic Children's Hospital Wilhelmstift, Hamburg, Germany; the [3]Division of Pediatric Endocrinology and Diabetology, Department of Pediatrics, University of Luebeck, University Hospital of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany; the [4]Department of Pediatrics, Medical University of Vienna, Vienna, Austria; the [5]Hospital for Children and Adolescents, University of Leipzig, Leipzig, Germany; the [6]Clinic of Paediatrics and Molecular Diabetes Research Group Experimental and Clinical Research Center, Berlin, Germany; the [7]Diabetes Center, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University of Bochum, Bad Oeynhausen, Germany; and the [8]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany.
Corresponding author: Paul-Martin Holterhus, holterhus@pediatrics.uni-kiel.de.
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Continuous subcutaneous insulin infusion therapy (CSII) has become a major therapeutic approach for the treatment of type 1 diabetes including all pediatric age-groups since the late 90s of the last century (1,2). The prospective German Austrian DPV-Wiss database (3) currently contains 47,288 patients with type 1 diabetes aged <20 years, of whom 22.7% (10,752 patients) are on insulin pumps (DPV-Wiss, 2 July 2011). In our recent study based on 1,248 children on CSII (4), we discovered that pediatric diabetologists in specialized pediatric diabetes centers throughout Germany and Austria have independently developed a defined set of qualitatively distinct basal insulin patterns for their patients. One of the major characteristics of these patterns was the shift of the maximum basal insulin infusion rate (BR) in the early morning as seen in the pubertal and postpubertal children back to late evening as observed in younger children (4). Age-dependent BRs have been confirmed by descriptive analyses stratified by age-groups (5,6).

In contrast to multiple adjustments of the individual BR in a child starting CSII based on only anecdotal assumptions like a biphasic dawn-dusk (BC) pattern or any other arbitrary age-adjusted pattern, commencement of CSII in children will profit from a standardized and differentiated approach assigning an optimal pattern a priori. We here demonstrate that in 5,903 children from the DPV-Wiss database who started CSII only after our first study, virtually identical patterns were chosen by the diabetes teams as identified by an unsupervised hierarchical clustering strategy. We here show by logistic regression analysis that the probability of clustering within one of four major baseline insulin infusion patterns is mainly based on age, partly on duration of diabetes, and less on male or female sex. Calculated probabilities are mostly highly similar in our large new dataset (dataset 2) compared with the previous independent dataset (dataset 1).

RESEARCH DESIGN AND METHODS

—The German/Austrian DPV-Wiss database for quality-control

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and scientific surveys in pediatric diabetology (3) served as the data source. Data collection in DPV-Wiss is in compliance with the hospital data-protection agencies in all participating centers. Only anonymous data are transmitted for centralized analysis at the Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany.

We first retrieved all patients on CSII <20 years of age as documented in DPV-Wiss (November 2009) excluding all 1,248 individuals from our first study (4) (dataset 1) resulting in 6,063 CSII patients (dataset 2). Only the most recent BR individually adjusted during the course of diabetes was considered. BR data of patients using normal insulin instead of rapid-acting insulin analogs were corrected by 1 h. Mean ± SD age of patients in dataset 2 was 10.6 ± 4.3 years (12.6 ± 3.7 years in dataset 1). Age at onset of diabetes in dataset 2 was 6.6 ± 3.8 years (7.3 ± 3.7 years in dataset 1). Duration of diabetes was 4.0 ± 3.4 years in dataset 2 (5.2 ± 3.4 years in dataset 1). Dataset 2 contained 48% boys (43% boys in dataset 1). Secondly, we performed unsupervised hierarchical average linkage clustering of BR data as previously described (4,7) to sort the 6,063 dataset 2 children according to BR patterns.

Subsequently, we used logistic regression analysis to identify the prediction factors for clustering of individual patients in the distinct BR patterns. Because of the results from our previous study (4), we only considered age, duration of diabetes, and sex. We performed this calculation in both the new 6,063 patients (dataset 2) and the previous 1,248 patients (dataset 1). In order to be able to assess the probabilities of a patient for clustering in a distinct BR group, we then calculated the maximum probability estimates with the corresponding SEs, Wald χ^2, and *P* values for the parameters intercept, age, duration of diabetes, and sex—again, for both datasets 1 and 2.

To display the correlation of probabilities for clustering in a distinct BR cluster to age of the patient, duration of diabetes, and male or female sex, we created typical "test patients" and introduced their data into the following equations containing the respective dataset-specific and BR cluster–specific maximum probability estimates of either of the two datasets:

$$P(\text{girls}) = 1/(1 + e^{-[\text{estimate intercept}]-[\text{estimate age}]\times\text{age}-[\text{estimate duration of diabetes}]\times\text{duration of diabetes}})$$

$$P(\text{boys}) = 1/(1 + e^{-[\text{estimate intercept}]-[\text{estimate age}]\times\text{age}-[\text{estimate duration of diabetes}]\times\text{duration of diabetes}-[\text{estimate sex}]})$$

We used the following characteristics for the test patients: age 4, 8, 12, and 16 years; duration of diabetes 1, 2, 4, 8, and 12 years (where applicable); and assignment of either male or female sex.

RESULTS—Hierarchical clustering of the most recently documented BRs in the 6,063 CSII children of dataset 2 clearly confirmed the existence of distinct circadian patterns in 5,903 classifiable patients. One hundred and sixty patients did not sort into clusters. The heat map (Fig. 1) shows that the patients subdivided into four major patterns, thus condensing the previous, more diverse picture (4). A total of 2,490 patients (42.2%) showed a biphasic pattern with maximum insulin peaks at 5–6 A.M. and 5–6 P.M. and minimum insulin at 0–1 A.M. and 11–12 P.M. (cluster BC) (Fig. 1 and Supplementary Table 1). Mean age in this cluster was 12.8 years, thus representing the oldest age-group. The shape of the cluster corresponded well with clusters B and C in our previous work (dataset 1 [4]). A total of 2,154 patients (36.5%) clustered in a pattern with a continuous insulin rise in the evening lasting past midnight approaching a maximum at 5–6 A.M., corresponding with cluster D in our previous work (dataset 1 [4]) (cluster D) (Fig. 1 and Supplementary Table 1). Mean age in this group was 10.1 years. A total of 853 patients (14.5%) formed a cluster with a single insulin peak at 9–10 P.M. (cluster F) (Fig. 1 and Supplementary Table 1), which nicely reflected cluster F in dataset 1 (4). Mean age of this group was only 6.3 years, thus representing the youngest children. An inverse cluster was observed in 406 patients (6.9%) with a mean age of 8.7 years and a plateau of insulin during daytime from 9–10 A.M. to 7–8 P.M. (cluster AG) (Fig. 1 and Supplementary Table 1). This cluster represents a combination of the previous clusters A and G in dataset 1 (4).

Since age, duration of diabetes, and sex proved to be associated with differences in the assigned BR regimen (4), we used these variables for logistic regression analysis to identify prediction factors for clustering of individual patients in clusters F, AG, BC, or D, respectively. This procedure was undertaken for both dataset 2 and dataset 1. Age was a significant and by far the most striking prediction factor for all four BR patterns (Supplementary Table 2). Duration of diabetes played a less prominent role (Supplementary Table 2). Interestingly, having a BR pattern AG correlated significantly with female sex (Supplementary Table 2). This tendency was even more pronounced in the larger dataset 2 compared with the previous dataset 1. In summary, dataset 2 analyses were well in line with analyses based on the previous dataset 1 (Supplementary Table 2).

Based on calculation of the maximum probability estimates for each of the parameters (Supplementary Table 2), we introduced the corresponding data of our test patients into the prediction equation for each of the four BR patterns. We performed this procedure for both the new dataset 2 and the previous dataset 1 independently. Figure 2 underlines in general that age is indeed the most predominant predictor of having a certain BR pattern in both datasets. In particular, Fig. 2*A* demonstrates that the probability of having a pattern F BR is clearly linked to young age. Importantly, the curves for previous and new datasets are almost identical. Moreover, no obvious differences in the distribution of probabilities for BR F exist that rely on male or female sex in either dataset (Fig. 2*A* and Supplementary Table 3*A*). In contrast, Fig. 2*C* (see also Supplementary Table 3*C*) shows the inverse picture for the BR BC. Probability is clearly increasing with age, particularly at the age of ≥12 years. Interestingly, the overall probability of having a BR BC is slightly lower in the new dataset 2 than in the previous dataset 1, which might reflect the higher percentage of younger children on insulin pumps in dataset 2. Figure 2*D* shows that probability of BR D is also dependent on age and decreases slightly with increasing age. While boys and girls show virtually congruent curves in both datasets, there is a higher probability of having a BR D in dataset 2 compared with dataset 1 (Fig. 2*D* and Supplementary Table 3*D*). Since BR D children are again younger than the BC children, this finding most likely also reflects the change of the age distribution between the two datasets. The probability of BR pattern AG decreases with age, too (Fig. 2*B* and Supplementary Table 3*B*). This holds true for both independent datasets. However, patients in dataset 2 had a lower probability for this pattern than in dataset 1. Since this pattern likely compensates

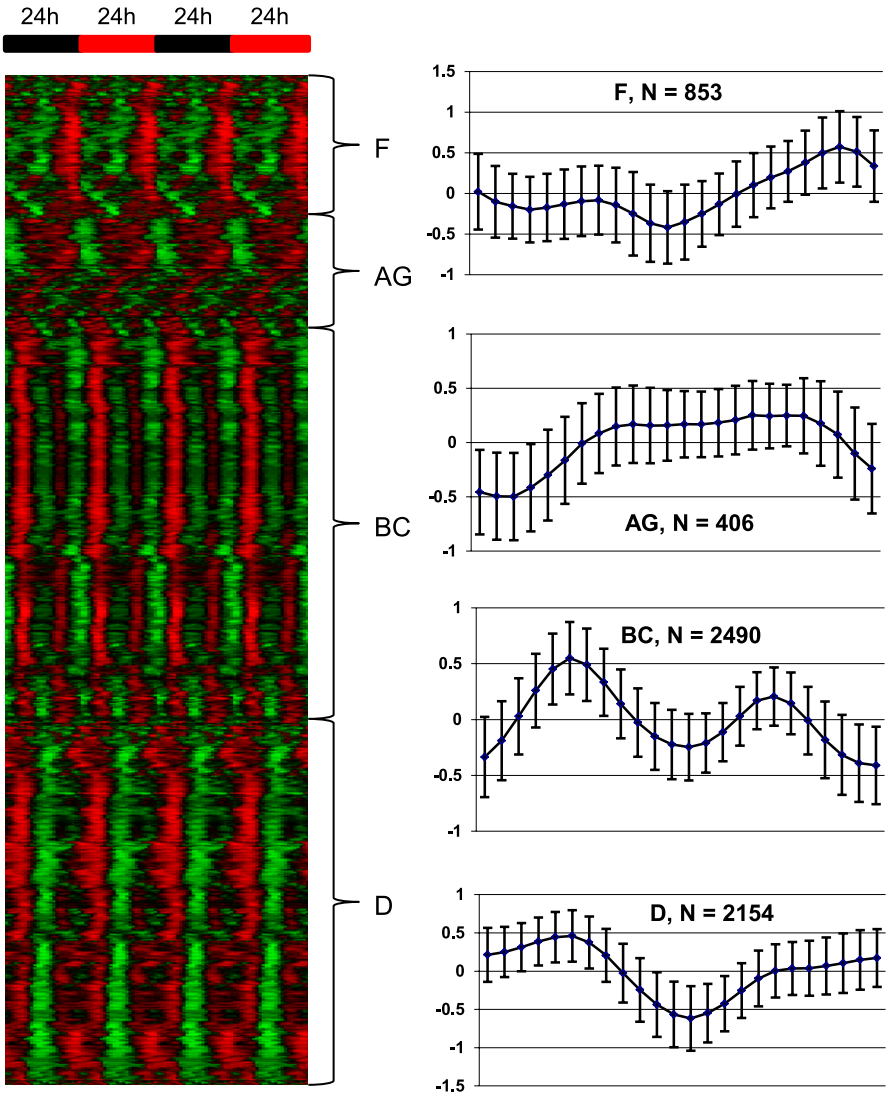

Figure 1—Left panel: *Data heat map based on unsupervised hierarchical average linkage clustering of the most recent BRs of 6,063 pediatric patients with type 1 diabetes treated with CSII. The patients have been sorted by clustering along the y-axis, while the time course of the BRs is displayed from* left *to* right *over a period of 4 × 24 h on the* x*-axis for visualization of the differences of patterns and circadian rhythms. Increasing red intensity represents increasing insulin infusion rates, while increasing green intensity represents decreasing insulin infusion rates. Blackish colors reflect BRs near an individual's mean BR. Clustering identifies the most similar BRs and sorts them right next to each other. The* right margin *of the heat map depicts the four leading BR patterns of the dataset, named F, AG, BC, and D.* Right panel: *mean BRs of all patients clustering in pattern F, AG, BC, or D and the variation from mean ± SD BR per pattern* (y*-axis) are displayed (mean BR = 1). (See also Supplementary Table 1.) The* x*-axis represents a 24-h interval from 0000 h to 2300 h.*

mealtime insulin with a high daytime BR, this observation might reflect a change in BR strategy applied in the diabetes centers. AG is the only BR pattern with a prominent sex difference, since girls have a higher probability of running on BR AG than boys in both datasets (Fig. 2*B* and Supplementary Table 3*B*).

CONCLUSIONS—We here demonstrate that in the largest cohort of children and adolescents with type 1 diabetes on CSII thus far reported in the literature, four major distinct BR patterns had been programmed by independent clinical diabetes teams during the course of diabetes. Logistic regression analysis revealed that unsupervised assignment of a child by hierarchical clustering to one of the four different BR patterns was obviously based on the same prediction factors in both independent datasets, i.e., age, to a much lesser extent duration of diabetes, and rarely sex. In essence, the youngest children showed the highest insulin infusion rates in the late evening before midnight (BR F), older school children had higher insulin at midnight up to the early morning (BR D), and pubertal children showed the typical dawn-dusk pattern (BR BC) (4). Therefore, and owing to the fact that in total >7,000 children had been investigated in both of our studies together, we conclude that these patterns likely represent a realistic approximation to the real age-dependent circadian distribution of insulin needs. One hundred and sixty patients of the study did not cluster into one of the four patterns. This may be due to particular therapeutic needs in individual patients or due to individual clinical situations. While we believe that the statistical bias is acceptable for the whole picture, these data point to the fact that in addition to characteristic BR patterns children with diabetes on CSII may have very variable metabolic needs to be handled by their BR.

Initiation of CSII and continuous clinical follow-up of a child with type 1 diabetes on insulin pump would profit significantly from knowledge and consideration of the individual circadian BR distribution. Therefore, we developed a mathematical prediction model that calculates the maximum probability for a given child to be treated with a certain BR pattern. In order to verify the biological significance, we performed these calculations independently in both of the two datasets. With use of test patients of a given age, duration of diabetes, and sex, the resulting probability curves were almost identical in the two datasets concerning BR F and BR BC reflecting the youngest and the oldest age-groups (Fig. 2*A* and *C*). Probabilities for assignment to patterns D and AG varied more between datasets 1 and 2 but generally showed the same age dependence (Fig. 2*B* and *D*). We conclude that this difference is most likely due to the differences in the age distribution of the two cohorts with younger children in dataset 2. The high similarity of the patterns and the good reproducibility of the probabilities for clustering to BR patterns comparing the two datasets support an overriding biological significance of our findings independent of the given cohort 1 or 2. The differences of the circadian distribution of insulin needs are likely to be due to the continuously changing neuroendocrine hormonal background from early childhood to

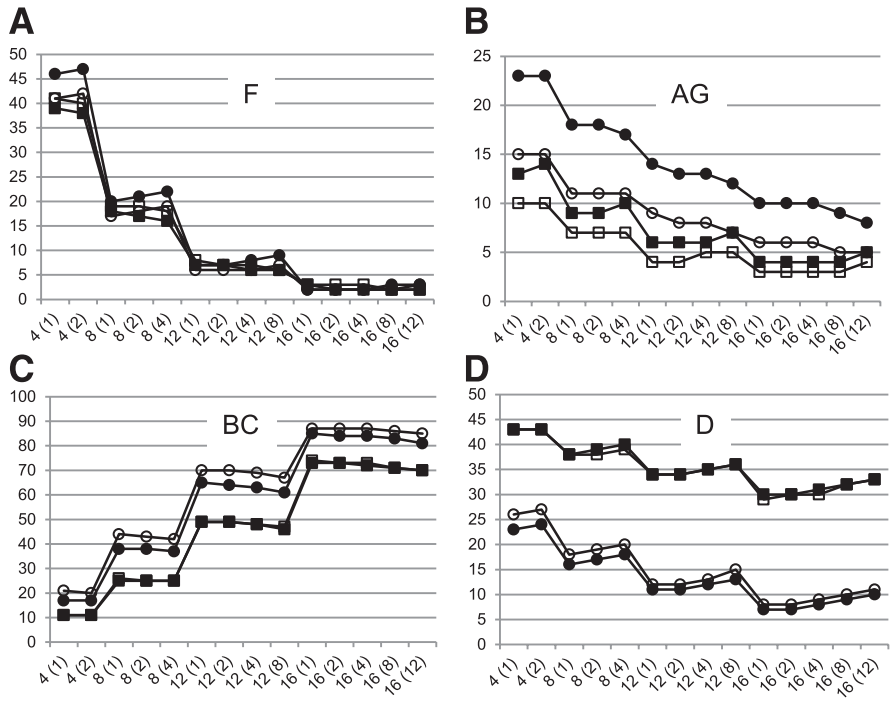

Figure 2—*Calculation of probabilities for typical patients of being treated with a BR pattern F* (A)*, AG* (B)*, BC* (C)*, and D* (D)*, respectively. The* y*-axis represents the probability for each of the four patterns in percent. (See also Supplementary Table 3*A–D.*) Age and duration of diabetes (in parenthesis) are given on the* x*-axis. ●, girls (dataset 1); ○, boys (dataset 1); ■, girls (dataset 2); □, boys (dataset 2).*

adolescence, e.g., changing sleep patterns influencing growth hormone secretion in the small child, changing physical activity, growth, body proportions, growth spurt, puberty, and sex steroids (4,8–13). In this sense, increasing sex steroid secretion during puberty of a child with type 1 diabetes on CSII enhancing growth hormone secretion during the night would increase early morning insulin resistance resulting in higher insulin needs and, hence, a higher probability of being treated with a BC BR pattern. We conclude that based on our mathematical model, it is possible to predict a "best fit" BR pattern for individual children with type 1 diabetes treated with CSII.

Continuous glucose monitoring by glucose sensors is at the advent of a revolution in CSII treatment in children with type 1 diabetes (14–17). Furthermore, different diabetes research groups all over the world work on closing the loop between continuous glucose sensing and insulin delivery via insulin pumps (18–20). A perfect system would actually act completely automatically like the healthy β cells of the normal pancreas. One of several difficult tasks to solve is programming suitable computer algorithms (21–24) matching subcutaneous insulin delivery via the pump with the continuous physiological changes of insulin sensitivity and insulin needs during the course of day and night. We suggest that our large-scale data provide valuable information for modulating mathematical prediction models in closed-loop algorithms by providing relevant information on age-dependent changes and circadian variation of insulin sensitivity in children. In this context, our prediction equations could be used to approximate decision corridors for insulin delivery in individual children set on closed-loop CSII.

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P.-M.H. contributed data, developed the research strategy, performed statistical analyses, and wrote the manuscript. J.B. contributed data, contributed expert advice on CSII, and reviewed and edited the manuscript. F.R. contributed data and reviewed and edited the manuscript. B.H. contributed data, contributed expert advice on CSII, and edited the manuscript. V.W. contributed data and reviewed and edited the manuscript. B.R.-M. reviewed and edited the manuscript. T.K. contributed data, contributed expert advice on CSII in children, and reviewed the manuscript. K.R. contributed data and reviewed and edited the manuscript. W.Q. contributed data, contributed expert advice on CSII in childhood, and reviewed and edited the manuscript. R.H. performed statistical analyses and wrote, reviewed, and edited the manuscript as senior author. P.-M.H. and R.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX—The network of Austrian and German pediatric diabetes centers contributing to the DPV-Wiss database consists of the following centers: Aachen-Innere RWTH; Aachen-Uni-Kinderklinik RWTH; Aalen Kinderklinik; Ahlen St. Franziskus Kinderklinik; Altötting Zentrum Inn-Salzach; Altötting-Burghausen Innere Medizin; Arnsberg-Hüsten Karolinenhosp; Kinderabteilung; Asbach Kamillus-Klinik Innere; Aue Helios Kinderklink; Augsburg Innere; Augsburg Kinderklinik Zentralklinikum; Aurich Kinderklinik; Bad Aibling Internist; Praxis; Bad Driburg/Bad Hermannsborn Innere; Bad Hersfeld Kinderklinik; Bad Kreuznach-St. Marienwörth Innere; Bad Kösen Kinder-Rehaklinik; Bad Lauterberg Diabeteszentrum Innere; Bad Mergentheim–Diabetesfachklinik; Bad Mergentheim–Gemeinschaftspraxis DM-dorf Althausen; Bad Oeynhausen Herz-und Diabeteszentrum NRW; Bad Orb Spessart Klinik; Bad Reichenhall Kreisklinik Innere Med.; Bad Salzungen Kinderklinik; Bad Säckingen Hochrheinklinik Innere; Bad Waldsee Kinderarztpraxis; Bautzen Oberlausitz KK; Bayreuth Innere Medizin; Berchtesgaden CJD; Berchtesgaden MVZ Innere Med; Berlin DRK-Kliniken; Berlin Endokrinologikum; Berlin Evang; Krankenhaus Königin

Elisabeth; Berlin Kinderklinik Lindenhof; Berlin Klinik St. Hedwig Innere; Berlin Oskar Zieten Krankenhaus Innere; Berlin Schlosspark-Klinik Innere; Berlin St. Josephskrankenhaus Innere; Berlin Virchow-Kinderklinik; Berlin Vivantes Hellersdorf Innere; Bielefeld Kinderklinik Gilead; Bocholt Kinderklinik; Bochum Universitätskinderklinik St. Josef; Bonn Uni-Kinderklinik; Bottrop Kinderklinik; Bottrop Knappschaftskrankenhaus Innere; Braunschweig Kinderarztpraxis; Bremen–Kinderklinik Nord; Bremen–Mitte Innere; Bremen Kinderklinik St. Jürgenstrasse; Bremen-Epidemiologieprojekt; Bremerhaven Kinderklinik; Böblingen Kinderklinik; Celle Kinderklinik; Chemnitz Kinderklinik; Chemnitz-Hartmannsdorf Innere Medizin-DIAKOMED-1; Coesfeld Kinderklinik; Coesfeld/Dülmen Innere Med.; Darmstadt Innere Medizin; Darmstadt Kinderklinik Prinz. Margareth; Datteln Vestische Kinderklinik; Deggendorf Kinderarztpraxis; Deggendorf Kinderklinik; Deggendorf Medizinische Klinik II; Delmenhorst Kinderklinik; Detmold Kinderklinik; Dornbirn Kinderklinik; Dortmund Kinderklinik; Dortmund Knappschaftskrankenhaus Innere; Dortmund Medizinische Kliniken Nord; Dortmund-St. Josefshospital Innere; Dresden Neustadt Kinderklinik; Dresden Uni-Kinderklinik; Duisburg Evang. und Johanniter Krhs, Innere; Duisburg Malteser St. Anna Innere; Duisburg Malteser St. Johannes; Düren-Birkesdorf Kinderklinik; Düsseldorf Uni-Kinderklinik; Eberswalde Klinikum Barnim Werner Forßmann–Innere; Erfurt Kinderklinik; Erlangen Uni Innere Medizin; Erlangen Uni-Kinderklinik; Essen Diabetes-Schwerpunktpraxis Dr. Best; Essen Elisabeth Kinderklinik; Essen Uni-Kinderklinik; Esslingen Städtische Kinderklinik; Eutin Kinderklinik; Eutin St.-Elisabeth Innere; Frankenthal Kinderarztpraxis; Frankfurt Bürgerhospital; Frankfurt Uni-Kinderklinik; Frankfurt Uni-Klinik Innere; Freiburg Uni Innere; Freiburg Uni-Kinderklinik; Friedberg Innere Klinik; Friedrichshafen Kinderklinik; Fulda Innere Medizin; Fulda Kinderklinik; Fürth Kinderklinik; Gaissach Fachklinik der Deutschen Rentenversicherung Bayern Süd; Garmisch-Partenkirchen Kinderklinik; Geislingen Klinik Helfenstein Innere; Gelnhausen Innere; Gelnhausen Kinderklinik; Gelsenkirchen Kinderklinik Marienhospital; Gera Kinderklinik; Gießen Ev. Krankenhaus Mittelhessen; Gießen Uni-Kinderklinik; Graz Universitäts-Kinderklinik; Göppingen Innere Medizin; Göppingen Kinderklinik am Eichert; Görlitz Städtische Kinderklinik; Göttingen Uni-Kinderklinik; Güstrow Innere; Hachenburg Kinderpraxis; Hagen Kinderklinik; Halle Uni-Kinderklinik; Halle-Dölau Städtische Kinderklinik; Hamburg Altonaer Kinderklinik; Hamburg Endokrinologikum; Hamburg Kinderklinik Wilhelmstift; Hamburg-Nord Kinder-MVZ; Hameln Kinderklinik; Hamm Kinderklinik; Hanau Kinderklinik; Hanau St. Vincenz–Innere; Hannover Henriettenstift–Innere; Hannover Kinderklinik MHH; Hannover Kinderklinik auf der Bult; Haren Kinderarztpraxis; Heide Kinderklinik; Heidelberg Uni-Kinderklinik; Heidelberg Uniklinik Innere; Heidenheim Arztpraxis Allgemeinmed; Heidenheim Kinderklinik; Heilbronn Innere Klinik; Heilbronn Kinderklinik; Herdecke Kinderklinik; Herford Innere Kardiologie; Herford Kinderarztpraxis; Herford Klinikum Kinder & Jugendliche; Heringsdorf Inselklinik; Hermeskeil Kinderpraxis; Herne Evan; Krankenhaus Innere; Herten St. Elisabeth Innere Medizin; Herzberg Kreiskrankenhaus Innere; Hildesheim Innere; Hildesheim Kinderarztpraxis; Hildesheim Klinikum Kinderklinik; Hinrichsegen-Bruckmühl Diabetikerjugendhaus; Hof Kinderklinik; Homburg Uni-Kinderklinik Saarland; Idar Oberstein Innere; Ingolstadt Klinikum Innere; Innsbruck Universitätskinderklinik; Iserlohn Innere Medizin; Itzehoe Kinderklinik; Jena Uni-Kinderklinik; Kaiserslautern-Westpfalzklinikum Kinderklinik; Karlsburg Klinik für Diabetes & Stoffwechsel; Karlsruhe Städtische Kinderklinik; Kassel Kinderklinik Park Schönfeld; Kassel Rot-Kreuz-Krankenhaus Innere; Kassel Städtische Kinderklinik; Kaufbeuren Innere Medizin; Kempen Heilig Geist–Innere; Kiel Städtische Kinderklinik; Kiel Universitäts-Kinderklinik; Kirchen DRK Klinikum Westerwald, Kinderklinik; Kirchheim-Nürtingen Innere; Kleve Innere Medizin; Koblenz Kemperhof 1. 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Klinik; Koblenz Kinderklinik Kemperhof; Konstanz Innere Klinik; Konstanz Kinderklinik; Krefeld Innere Klinik; Krefeld Kinderklinik; Kreischa-Zscheckwitz, Klinik Bavaria; Köln Kinderklinik Amsterdamerstrasse; Köln Uni-Kinderklinik; Landau/Annweiler Innere; Landshut Kinderklink; Leipzig Uni-Kinderklinik; Leverkusen Kinderklinik; Limburg Innere Medizin; Lindenfels Luisenkrankenhaus Innere; Lingen Kinderklinik St. Bonifatius; Linz Innere Medizin; Linz Kinderklinik; Lippstadt Evangelische Kinderklinik; Ludwigsburg Innere Medizin; Ludwigsburg Kinderklinik; Ludwigshafen Kinderklinik St.Anna-Stift; Lübeck Uni-Kinderklinik; Lübeck Uni-Klinik Innere Medizin; Lüdenscheid Kinderklinik; Lünen Klinik am Park; Magdeburg Städtisches Klinikum Innere; Magdeburg Uni-Kinderklinik; Mainz Uni-Kinderklinik; Mannheim-Innere; Mannheim Uni-Kinderklinik; Marburg Uni-Kinderklinik; Marburg Uniklinik Innere Medizin; Mechernich Kinderklinik; Memmingen Kinderklinik; Merzig Kinderklinik; Minden Kinderklinik; Moers-St. Josefskrankenhaus Innere; Moers Kinderklinik; Mutterstadt Kinderarztpraxis; Mödling Kinderklinik; Mölln Reha-Klinik Hellbachtal; Mönchengladbach Kinderklinik Rheydt Elisabethkrankenhaus; Mühlacker Enzkreiskliniken Innere; Mühldorf Gemeinschaftspraxis; München 3; Orden Kinderklinik; München Diabetes-Zentrum Süd; München Kinderarztpraxis; München von Haunersche Kinderklinik; München-Gauting Kinderarztzentrum; München-Harlaching Kinderklinik; München-Schwabing Kinderklinik; Münster St. Franziskus Kinderklinik; Münster Uni-Kinderklinik; Münster pädiat. Schwerpunktpraxis; Nagold Kreiskrankenhaus Innere; Nauen Havellandklinik; Neuburg Kinderklinik; Neunkirchen Innere Medizin; Neunkirchen Marienhausklinik Kohlhof Kinderklinik; Neuss Lukaskrankenhaus Kinderklinik; Neuwied Kinderklinik Elisabeth; Neuwied Marienhaus Klinikum St. Elisabeth Innere; Nidda Bad Salzhausen Klinik Rabenstein/Innere-1 Reha; Nidda Bad Salzhausen Klinik Rabenstein/Innere-2 Reha; Nürnberg Cnopfsche Kinderklinik; Nürnberg Zentrum f. Neugeb., Kinder & Jugendl.; Oberhausen Innere; Oberhausen Kinderklinik; Oberhausen Kinderpraxis; Offenbach/Main Kinderklinik; Offenburg Kinderklinik; Oldenburg Kinderklinik; Oldenburg Schwerpunktpraxis; Oschersleben MED-IGREIF Bördekrankenhaus; Osnabrück Kinderklinik; Osterkappeln Innere; Ottobeuren Kreiskrankenhaus; Oy-Mittelberg Hochgebirgsklinik Kinder-Reha; Paderborn St. Vincenz Kinderklinik; Papenburg Marienkrankenhaus Kinderklinik; Passau Kinderarztpraxis; Passau Kinderklinik; Pforzheim Kinderklinik; Pfullendorf Innere Medizin; Pirmasens Städtisches Krankenhaus Innere; Plauen Vogtlandklinik Innere; Prenzlau Krankenhaus Innere; Rastatt Gemeinschaftspraxis; Rastatt Kreiskrankenhaus Innere; Ravensburg Kinderklink St. Nikolaus; Recklinghausen

Dialysezentrum Innere; Regensburg Kinderklinik St. Hedwig; Remscheid Kinderklinik; Rendsburg Kinderklinik; Reutlingen Kinderarztpraxis; Reutlingen Kinderklinik; Reutlingen Klinikum Steinenberg Innere; Rheine Mathiasspital Kinderklinik; Rosenheim Innere Medizin; Rosenheim Kinderklinik; Rosenheim Schwerpunktpraxis; Rostock Uni-Kinderklinik; Rostock Universität Innere Medizin; Rotenburg/Wümme Kinderklinik; Rüsselsheim Kinderklinik; Saaldorf-Surheim Diabetespraxis; Saalfeld Thüringenklinik Kinderklinik; Saarbrücken Kinderklinik Winterberg; Saarlouis Kinderklinik; Scheidegg Reha-Kinderklinik Maximilian; Schw. Gmünd Stauferklinik Kinderklinik; Schweinfurt Kinderklinik; Schwerin Innere Medizin; Schwerin Kinderklinik; Schwäbisch Hall Diakonie Innere Medizin; Schwäbisch Hall Diakonie Kinderklinik; Siegen Kinderklinik: Singen-Hegauklinik Kinderklinik; Sinsheim Innere; Spaichingen Innere; St. Augustin Kinderklinik; St. Pölten Kinderklinik; Stade Kinderklinik; Stolberg Kinderklinik; Stuttgart Olgahospital Kinderklinik; Suhl Kinderklinik; Sylt Rehaklinik; Tettnang Innere Medizin; Timmendorfer Strand, Curschmann-Klinik; Traunstein, Diabetologische Schwerpunktpraxis; Trier Kinderklinik der Borromäerinnen; Trostberg Innere; Tübingen Uni-Kinderklinik; Ulm Endokrinologikum; Ulm Schwerpunktpraxis Bahnhofsplatz; Ulm Uni-Kinderklinik; Vechta Kinderklinik; Viersen Kinderklinik; Villingen-Schwenningen Schwarzwald-Baar-Klinikum Innere; Waiblingen Kinderklinik; Waldshut Kinderpraxis; Waldshut-Tiengen Kinderpraxis Biberbau; Weiden Kinderklinik; Weingarten Kinderarztpraxis; Weisswasser Kreiskrankenhaus; Wernberg-Köblitz SPP; Wetzlar Diabetologische Schwerpunktpraxis; Wetzlar/Braunfels Innere; Wien Uni-Kinderklinik; Wiesbaden Horst-Schmidt-Kinderkliniken; Wiesbaden Kinderklinik DKD; Wilhelmshaven Reinhard-Nieter-Kinderklinik; Wilhelmshaven St. Willehad Innere; Wittenberg Kinderklinik; Wolgast Kinderklinik; Worms Kinderklinik; and Wuppertal Kinderklinik.

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