

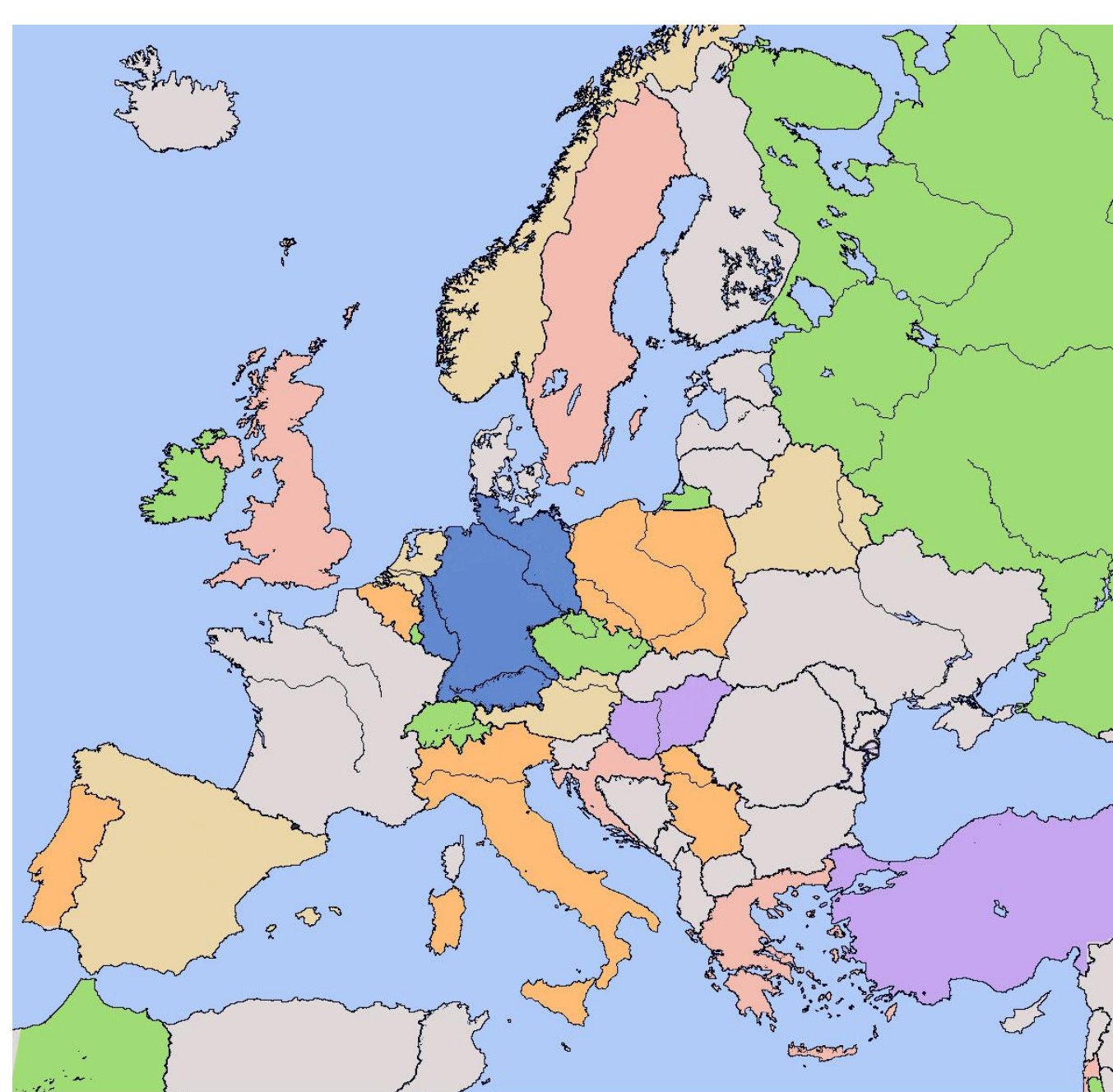
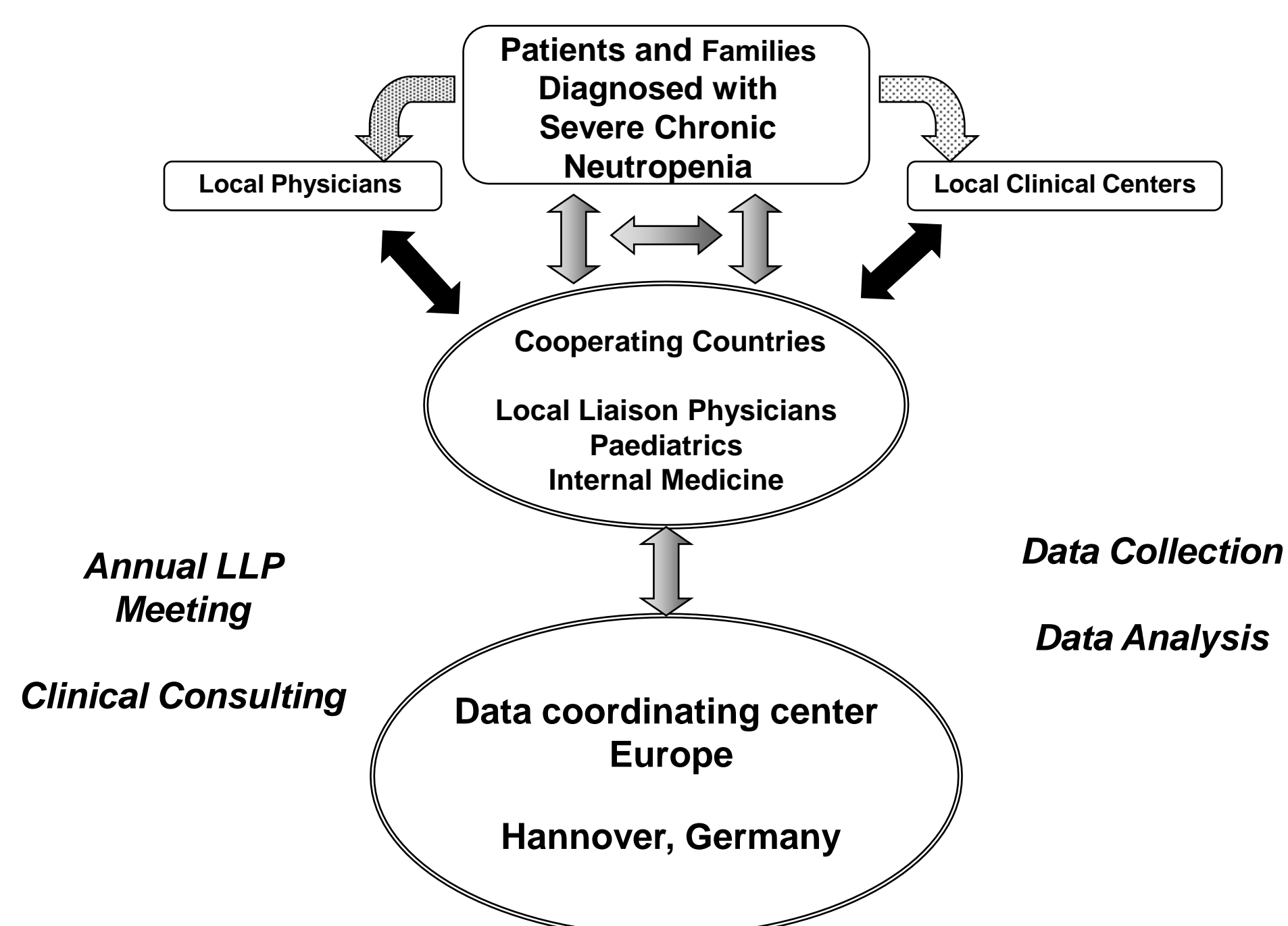
THE EUROPEAN BRANCH OF THE SEVERE CHRONIC NEUTROPENIA INTERNATIONAL REGISTRY: GENETIC AND PHENOTYPIC CHARACTERISTICS OF A HETEROGENOUS GROUP OF DISORDERS.

C. Zeidler, G. Pracht, M. Germeshausen, K. Welte, for the Severe Chronic Neutropenia International Registry (SCNIR) Hannover, Germany.

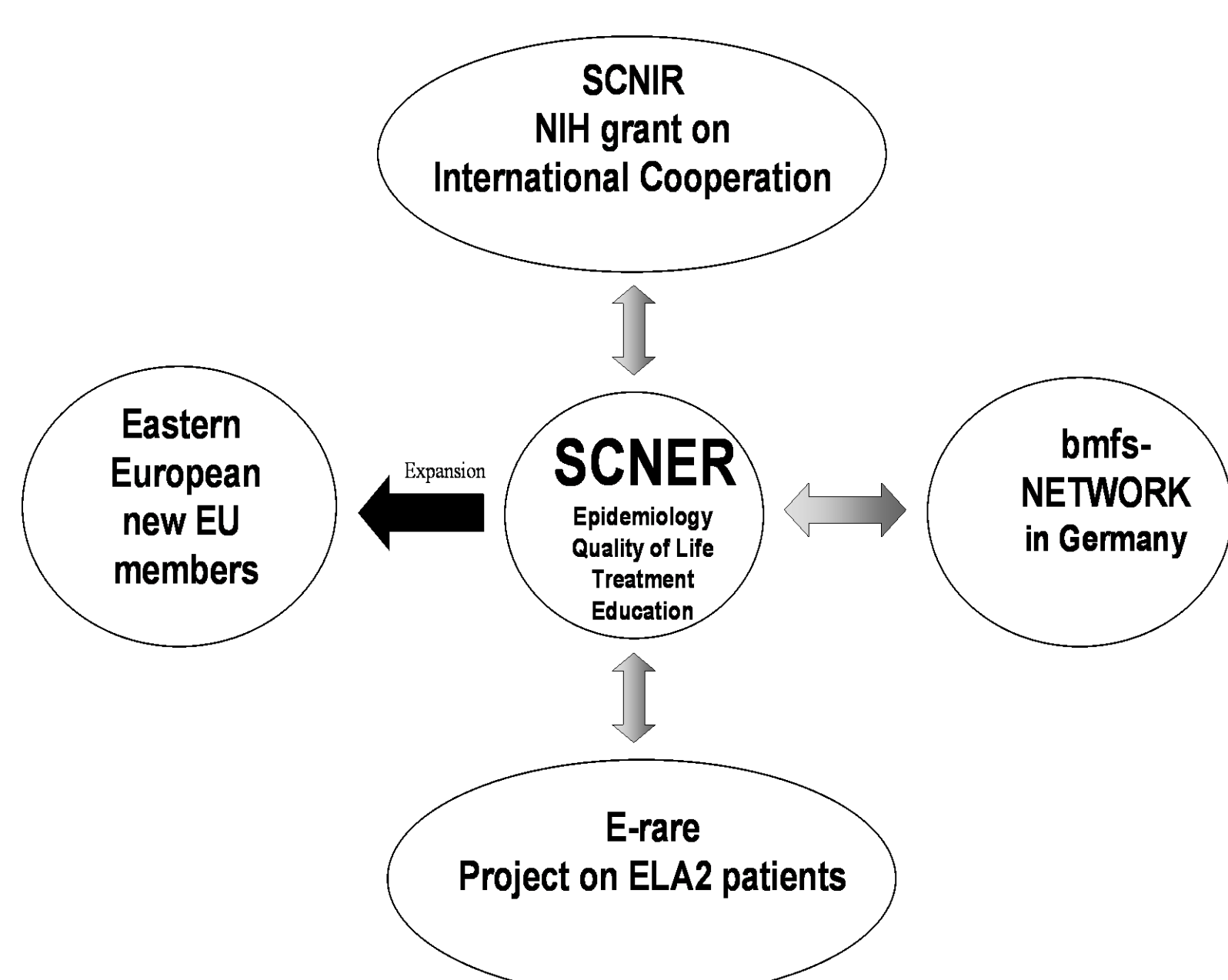
INTRODUCTION

Severe congenital neutropenia (CN) stands for a group of disorders characterized by extremely low neutrophil counts (ANC < 0.5x10⁹), early stage maturation arrest of myelopoiesis and recurrent bacterial infections. In general more than 90% of CN patients respond to daily G-CSF treatment with a sustained neutrophil increase resulting in significantly reduced infections and an improved quality of life. Besides neutropenia, the differences in treatment response and the presence of various concomitant clinical features in subpopulations of patients in conjunction with an increased risk of leukemic transformation in about 10% of all CN patients strongly suggested to search for new sub diagnoses to identify patients at risk for leukemia. Within Europe the SCNIR has collected longitudinal clinical data on more than 493 patients with various causes of CN (289 congenital, 64 cyclic, 132 idiopathic and 8 others) from 23 countries. This unique resource of data was used to identify new genes, classify patients by genetic subtypes of CN, estimate their relative frequency and to correlate genetic subtypes with prognosis and outcome. To date more than 10 disease causing gene mutations could be identified in congenital neutropenia patients. In approximately 50-60% of all patients autosomal dominant mutations in the *ELANE* gene are present. Initial genotype-phenotype correlation identified a group of different genetic defects sharing a high risk of leukemic transformation in contrast to others with no increased risk of leukemia.

THE EUROPEAN NEUTROPENIA NETWORK



INTERNATIONAL STRUCTURE OF THE NEUTROPENIA NETWORK



DEMOGRAPHICS

| Country | Pts. | Country | Pts. |
|----------------|------------|-----------------|------|
| Total | 493 | | |
| Austria | 16 | The Netherlands | 14 |
| Belgium | 28 | Norway | 19 |
| Belarus | 2 | Poland | 5 |
| Croatia | 2 | Portugal | 2 |
| Czech Republic | 4 | Russia | 1 |
| Germany | 192 | Serbia | 2 |
| Greece | 12 | Spain | 20 |
| Ireland | 11 | Sweden | 29 |
| Israel | 11 | Switzerland | 8 |
| Italy | 40 | Turkey | 8 |
| Luxembourg | 2 | United Kingdom | 64 |
| Morocco | 1 | | |

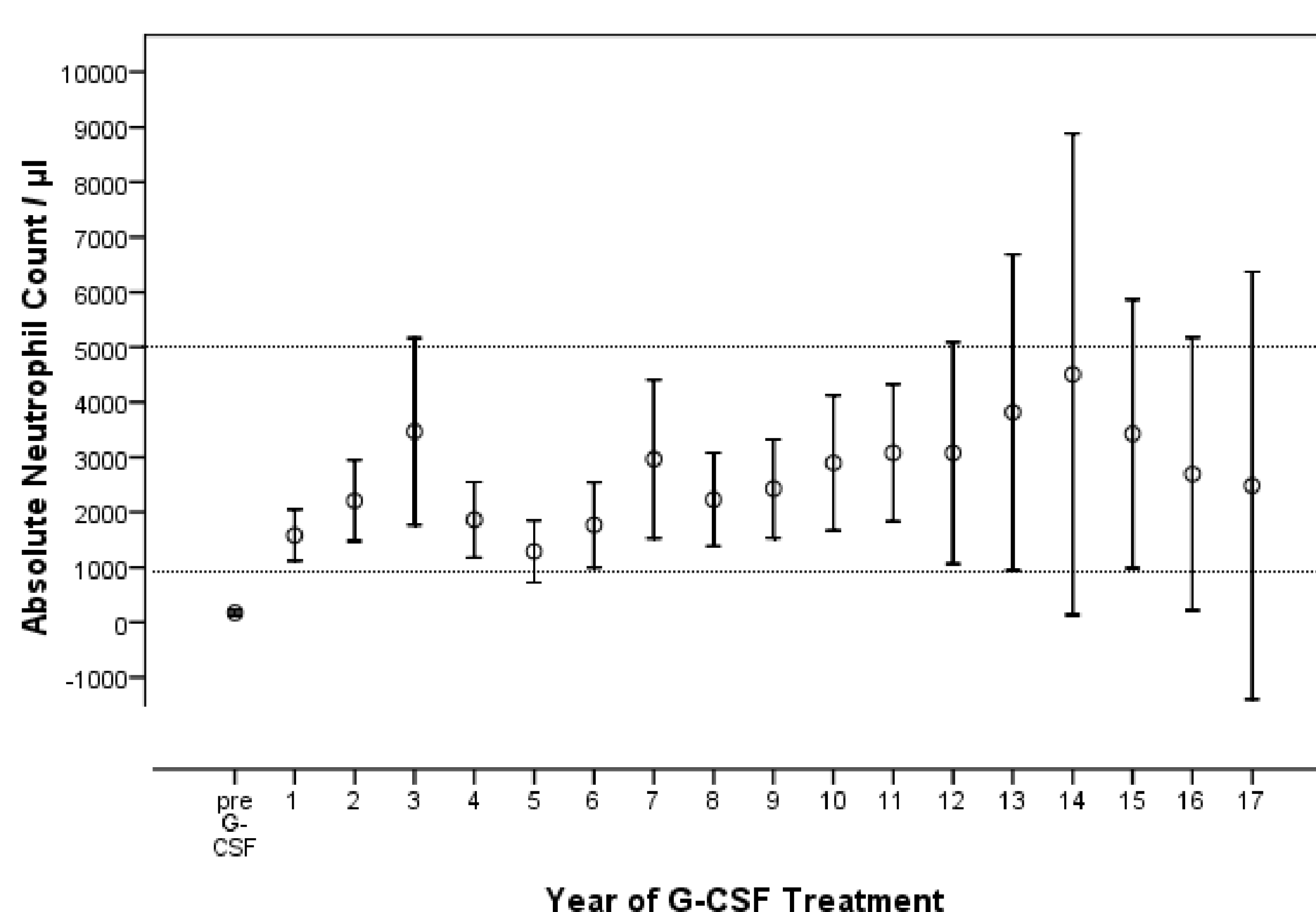
PATIENT CHARACTERISTICS GENETIC DISTRIBUTION

| Diagnosis | Pts. | Diagnosis | Pts. |
|---------------------------------|------------|-------------------------------|------------|
| Congenital neutropenia | 289 | Cyclic neutropenia | 64 |
| • Severe congenital NT | 71 | • ELANE mutation | 20 |
| • ELANE mutation | 66 | Idiopathic neutropenia | 82 |
| • HAX1 mutation | 23 | Autoimmune neutropenia | 50 |
| • ELANE neg/HAX1 neg | 35 | Others | 8 |
| • G6PC3 mutation | 8 | • Hyper-IgM syndrome | 3 |
| • WAS mutation | 2 | • LGL | 5 |
| • Shwachman Diamond Syndrome | 44 | | |
| • Glycogen storage disease Ib | 21 | | |
| • Congenital white Cell Aplasia | 1 | | |
| • Myelokathexis | 2 | | |
| • Barth Syndrome | 5 | | |
| • Cohen Syndrome | 1 | | |
| • P 14 mutation | 4 | | |
| • Pearson Syndrome | 1 | | |
| • WHIM Syndrome | 1 | | |
| • Unknown Syndrome | 4 | TOTAL | 493 |

G-CSF TREATMENT BY GENETIC SUBTYPE

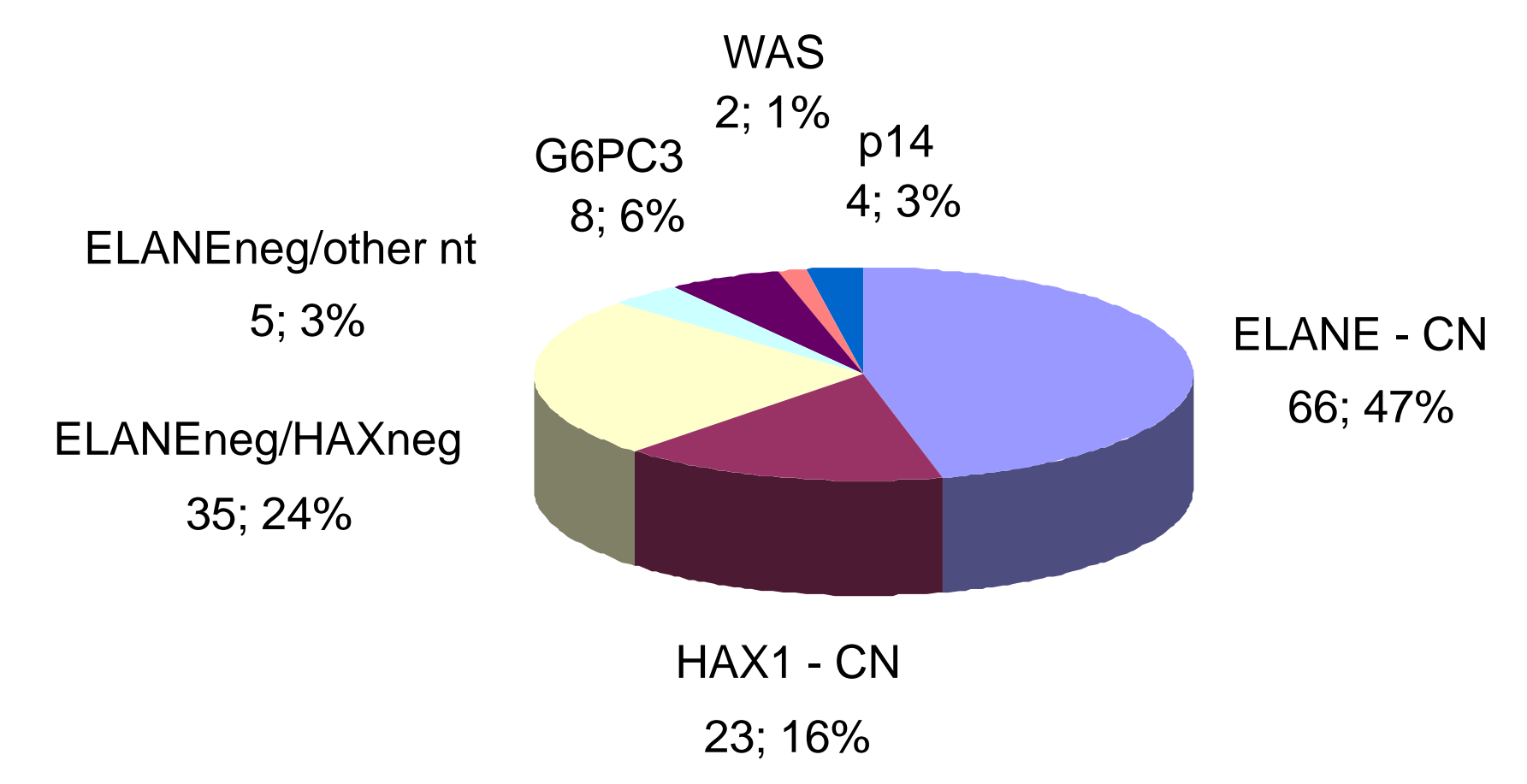
| Gene mutation | N | Median | Mean of Median | Std. Deviation of Median | Min. of Median | Max. of Median |
|----------------------|---------|--------|----------------|--------------------------|----------------|----------------|
| ELANE mutation | 63 / 66 | 8,92 | 16,95 | 26,051 | 0,9 | 120,00 |
| HAX1 mutation | 23 / 23 | 6,00 | 7,765 | 5,913 | 1,5 | 19,5 |
| ELANE neg / HAX1 neg | 32 / 35 | 5,945 | 19,38 | 33,519 | 0,87 | 180,00 |
| ELANE neg / other nt | 5 / 5 | 4,92 | 12,02 | 20,294 | 0,15 | 47,97 |
| G6PC3 mutation | 8 / 8 | 3,89 | 4,646 | 2,131 | 2,34 | 8,00 |
| P14 mutation | 4 / 4 | 5,18 | 5,043 | 0,622 | 4,19 | 5,6 |

COURSE OF NEUTROPHILS



LEUKEMIA IN GENETIC SUBGROUPS

| | Leukemia | | Total |
|---------------------------------|--------------------|-------------------|------------|
| | no count (%) | yes count (%) | |
| Congenital neutropenia | 253 (87,5%) | 36 (12,5%) | 289 |
| • Severe congenital NT | 62 (87,3%) | 9 (12,7%) | 71 |
| • ELANE mutation | 55 (83,3%) | 11 (16,7%) | 66 |
| • HAX1 mutation | 19 (82,6%) | 4 (17,4%) | 23 |
| • ELANE neg/HAX1 neg | 29 (82,9%) | 6 (17,1%) | 35 |
| • G6PC3 mutation | 8 (100,0%) | 0 | 8 |
| • WAS | 0 (0%) | 2 (100%) | 2 |
| • Shwachman Diamond Syndrome | 40 (90,9%) | 4 (9,1%) | 44 |
| • Glycogen storage disease Ib | 21 (100,0%) | 0 | 21 |
| • Other congenital neutropenias | 19 (100,0%) | 0 | 19 |
| Cyclic neutropenia | 63 (98,4%) | 1 (1,6%) | 64 |



CONCLUSIONS

- The identification of new CN subtypes, their distinctive risk of malignant transformation and the response to treatment has contributed substantially to our general understanding of neutropenia.
- Patients with severe congenital neutropenia who have mutations in the *ELANE*, *HAX1*, or *WAS* genes and also those with no recognized mutation are at risk of secondary leukemia.
- Despite mutations in the *ELANE* gene patients with cyclic neutropenia exhibit no increased risk for malignant transformation.
- So far, progression to MDS or leukemia has been described in the small number of cases with *G6PC3*- or *p14*-CN in our database.
- Mutational analysis is helpful to identify the genetic cause of severe congenital neutropenia but does not serve to identify patients at risk of leukemic transformation.
- New risk adapted strategies for diagnosis and treatment have to be implemented in the management of CN patients.

ACKNOWLEDGEMENT

- | | | |
|------------------------------|-----------------------------|----------------------------|
| Tore Abrahamsen (N) | Mirjana Gotic (YU) | Owen Smith (IRL) |
| Phil Ancliff (GB) | Aydan Ikinciogullari (TR) | Asbjørg Stray-Pedersen (N) |
| Marrie Bruin (NL) | Krzysztof Kalwak (PL) | Hannah Tamary (IL) |
| Göran Carlsson (S) | Antonios Kattamis (GR) | Adriana Teixeira (P) |
| Emília Cortesão (P) | Sally Kinsey (GB) | Geir E. Tjønnfjord (N) |
| Georg Ebetsberger (A) | Laszlo Marodi (H) | Fabio Tucci (I) |
| Cristina Díaz de Heredia (E) | Gundula Notheis (D) | Tatjana Uglova (BY) |
| Jean Donadieu (F) | Jan Palmblad (S) | Christiane Vermeylen (B) |
| Jan V. Droogenbroeck (B) | Helen Papadaki (GR) | Jaroslava Voglova (CZ) |
| Göran Elinder (S) | Theoni Petropoulou (GR) | Blanca Xicoy (E) |
| Piero Farrugia (I) | Sergey A. Roumiantsev (RUS) | Sonja Zweegmann (NL) |
| | Liudmila Shats (RUS) | |

THE EUROPEAN DATA COORDINATING CENTER IN HANNOVER:
Gusal Pracht, Stephanie King, Christiane Weyer, Cornelia Zeidler and Karl Welte
• www.schwere-chronische-neutropenie.de
• www.severe-chronic-neutropenia.org

We thank all colleagues associated with the Severe Chronic Neutropenia International Registry for their continued assistance. We are also grateful to the many physicians worldwide who faithfully and generously submitted data on their patients and the patients for their consent. Special thanks to those Colleagues who shared their data on the patients reported in this poster.