Guatemala: Cuidados de cáncer pediátrico, organización, resultados y retos del sistema de salud para reducir la mortalidad

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2 febrero, 2017
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1. Situación epidemiológica de Cáncer Pediátrico en Guatemala

- Incidencia, mortalidad, tasas de supervivencia y tendencias.

Cáncer Pediátrico en Guatemala; el pasado

- **1990-95 Datos Históricos**
- Falta de un Centro especializado
- 100 casos/año
- 42% abandono de tratamiento
- Menos de 20% sobrevivían a los 2 años del diagnóstico

Luna S, Slowing K, Valverde P, Antillon F, *et al*. Pediatric Cancer in Guatemala. A retrospective study. [abstract] Med Pediatr Oncol 1997;229:353.

¿Qué se hizo?

- **Fundación Ayúdame a Vivir (AYUVI) se crea en Mayo 1997**

- **Como resultado de la cooperación multistitucional se abre la Unidad Nacional de Oncología Pediátrica (UNOP), en Abril 2000**
- **0-17.9 años, sin costo para pacientes y sus familias**

Fundación Ayúdame a VIVIR
Salvando niños con cáncer
GUATEMALA

Ministerio de Salud Pública y Asistencia Social

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

Resultados

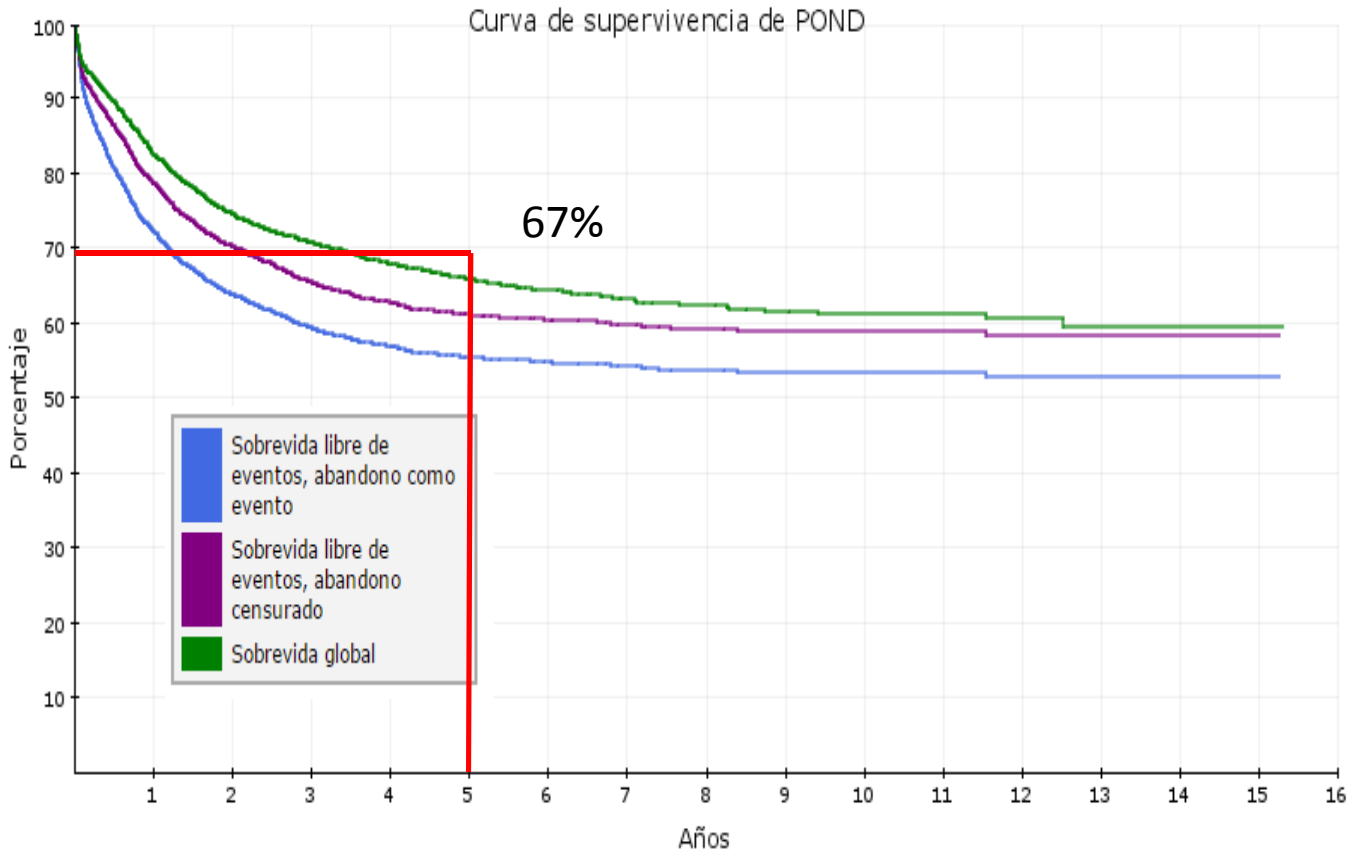
	1990-5 Pre-Progam	1998-9 HR	2000 UNOP	2007	2008	2009	2012	2013	2014	2015	2016
% Abandonment	42	25	17	8.2	3.5	2.3	2.2	1.5	1.0	1.7	0.7
OS all tumors	<20%	~40%	→	→	→	→	→	→	→		67%

Cases per year	100	110	129	280	287	302	407	406	405	461	432
Beds	-	-	28	→	→	→	→	→	60	65	65
Ped. Hem-Onc	0	1	3						6.5	7.5	8.5

Fuente: Registro Hospitalario, base de datos POND de UNOP.

SOBREVIDA GLOBAL

No. 3820/5067



Original Article

The Treatment of Childhood Acute Lymphoblastic Leukemia in Guatemala: Biologic Features, Treatment Hurdles, and Results

Federico G. Antillón, MD, MMM, PhD[1,2]; Jessica G. Blanco, MD[1,3]; Patricia D. Valverde, MD[1]; Mauricio Castellanos, MD[1]; Claudia P. Garrido, MD[1]; Veronica Girón, MD[1]; Tomas R. Letona, MD[1]; Emilia J. Osorio, MD[1]; Dyna A. Borrayo[1]; Ricardo A. Mack, MD[1]; Mario A. Melgar, MD[1]; Rodolfo Lorenzana, MD[4]; Raul C. Ribeiro, MD[5]; Monika Metzger, MD[5,6]; Valentino Conter, MD[6,7]; Emanuela Rossi, PhD[3]; and Maria Grazia Valsecchi, PhD[3]

BACKGROUND: The National Pediatric Oncology Unit (UNOP) is the only pediatric hemato-oncology center in Guatemala. **METHODS:** Patients ages 1 to 17 years with acute lymphoblastic leukemia (ALL) were treated according to modified ALL Intercontinental Berlin-Frankfurt-Münster (IC-BFM) 2002 protocol. Risk classification was based on age, white blood cell count, immunophenotype, genetics (when available), and early response to therapy. **RESULTS:** From July 2007 to June 2014, 787 patients were treated, including 160 who had standard-risk ALL, 450 who had intermediate-risk ALL, and 177 who had high-risk ALL. The induction death rate was 6.6%, and the remission rate was 92.9%. The rates of death and treatment abandonment during first complete remission were 4.8% and 2.5%, respectively. At a median observation time of 3.6 years, and with abandonment considered an event, the 5-year event-free survival and overall survival estimates (±standard error) were 56.2% ± 2.1% and 64.1% ± 2.1%, respectively, with a 5-year cumulative incidence of relapse of 28.9% ± 2.0%. Twenty-one of 281 patients (7.5%) investigated were positive for the ets variant 6/runt-related transcription factor 1 (*ETV6/RUNX1*) fusion. **CONCLUSIONS:** A well organized center in a low-middle-income country can overcome the disadvantages of malnutrition and reduce abandonment. Outcomes remain suboptimal because of late diagnosis, early death, and a high relapse rate, which may have a partly genetic basis. Earlier diagnosis, better management of complications, and better knowledge of ALL will improve outcomes. ***Cancer* 2016;000:000–000.** © *2016 American Cancer Society.*

KEYWORDS: acute lymphoblastic leukemia, chemotherapy, childhood, low-middle-income countries, nutritional status.

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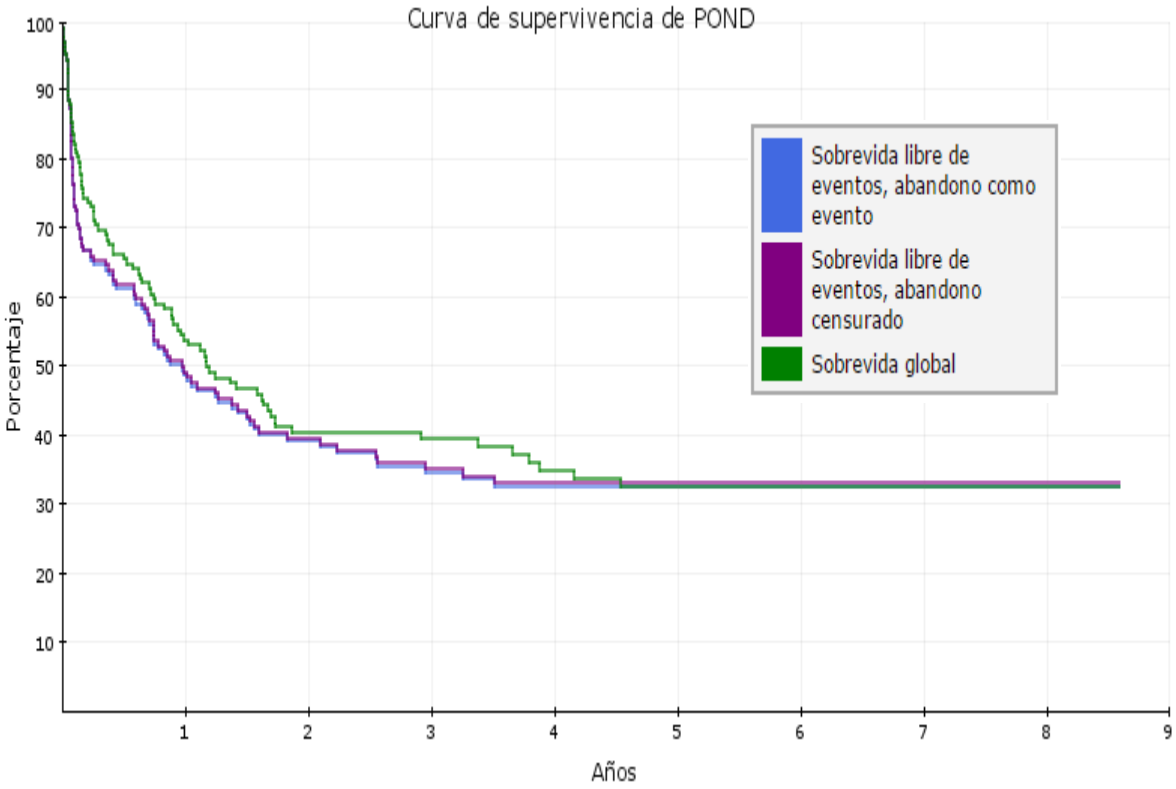
Sobrevida
Leucemia Mieloide Aguda
Enero 2007-Diciembre 2015
(No. = 155)

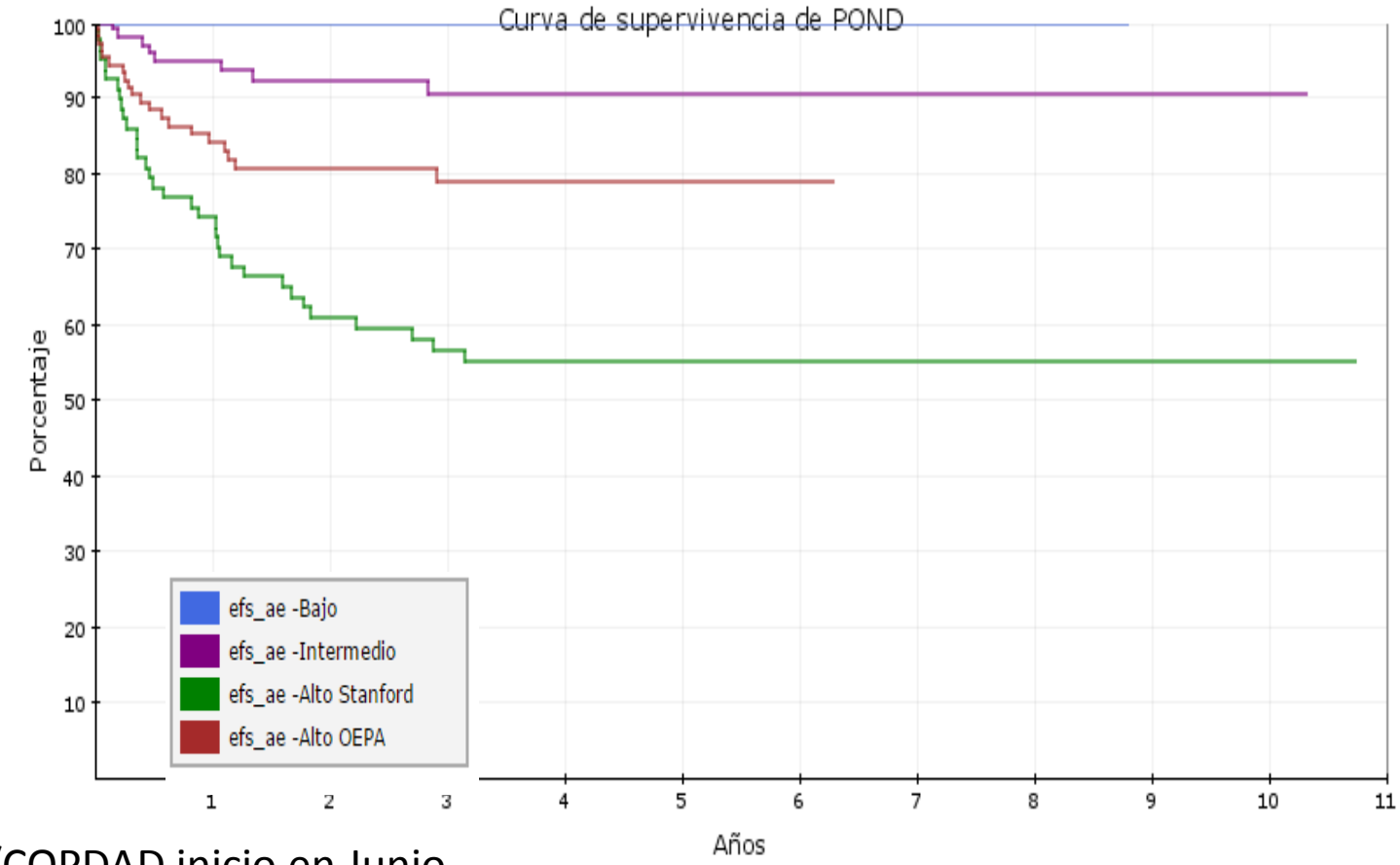


32%

Sobrevida Libre de Eventos,ae, L. Hodgkin

(Bajo=17)(Intermedio=95)(Alto Stanford=77)(Alto OEPA=102)

Agosto 2004 – Diciembre 2015

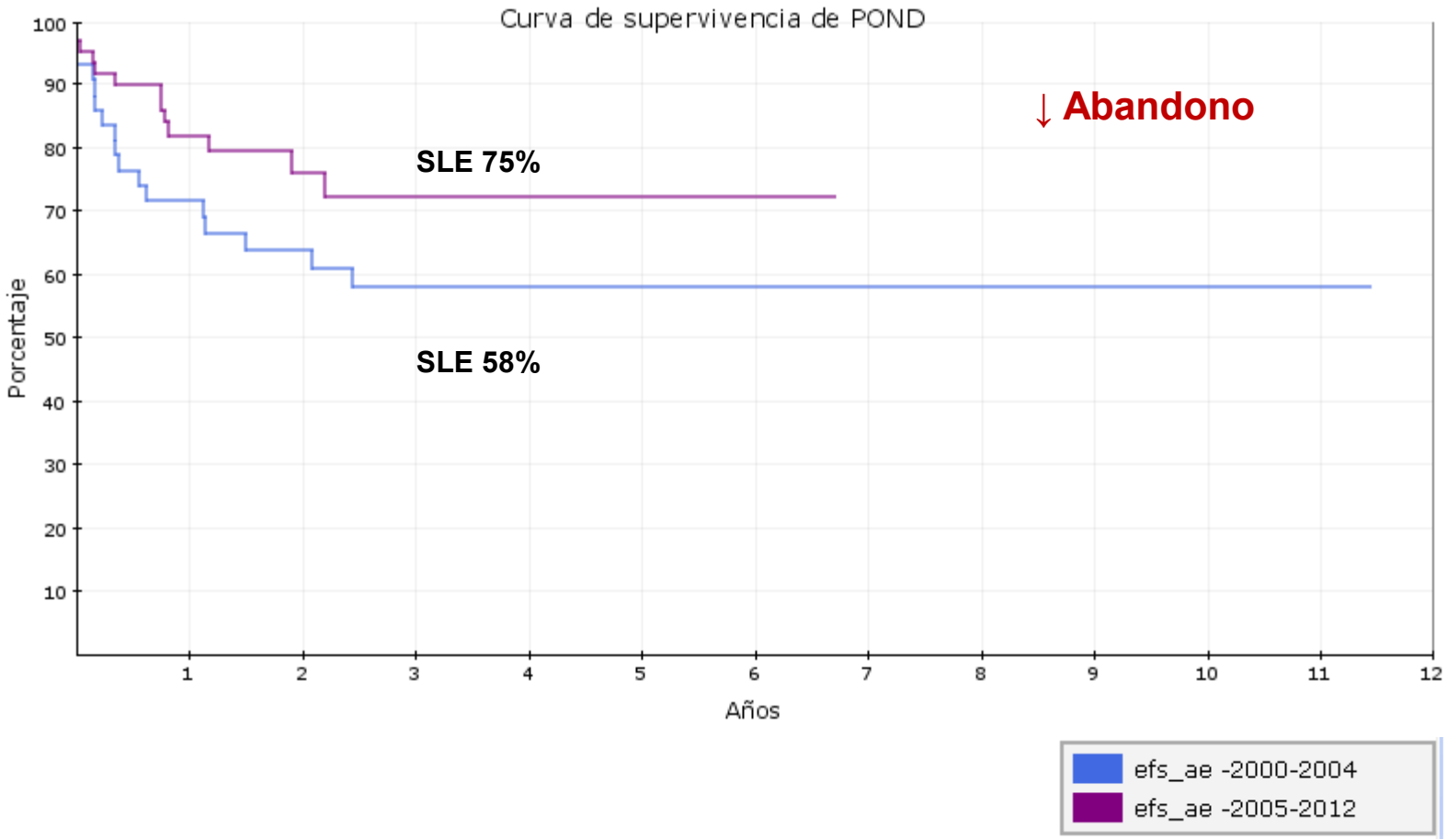


OEPA/COPDAD inicio en Junio 2009

STANFORD inicio Agosto 2004-Mayo 2009

Tumor Wilms dos eras (NWTSV/COG)

(2000 – 2004 No.= 41) (2005 – 2010 No.= 60)
(Total No.= 101)



Tasa por Región (por Millón de habitantes) Casos registrados, esperados y faltantes

REGION	Tasa por región	Casos registrados	Casos esperados	Casos faltantes
Metropolitano	119.5	120	121	0
Norte	32.1	22	82	-60
Nororiente	79.0	40	60	-20
Suroriente	59.4	30	61	-31
Central	80.6	56	83	-27
Suroccidente	73.2	119	194	-76
Noroccidente	50.6	53	127	-73
Petén	45.6	15	40	-25
Pais	72.0	455	769	-313

Documentados con Confirmación Histológica (No. 1383)

Número	%
1287	93%
96	7%
1383	100%

Genomic characterization of Childhood Acute Lymphoblastic Leukemia in Native American populations in Guatemala

Federico Antillon-Klussmann[1], Virginia Perez-Andreu[2], Cesar Rolando Najera Villagran[1], Dyna Borrayo[1], Karen Fernandez[3], Sohini Ramachandran[4],
Priyanka Nakka[4], Raul Ribeiro[5], Pedro A. de Alarcon[3], Jun J. Yang[2].
[1]Unidad Nacional de Oncología Pediátrica, Guatemala City, Guatemala. Department of [2]Pharmaceutical Sciences and [5]Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA. [3]Department of Pediatrics, University of Illinois College of Medicine at Peoria, Peoria, Illinois, [4]Department of Ecology and Evolutionary Biology, Brown University, Providence, Rhode Island, USA.

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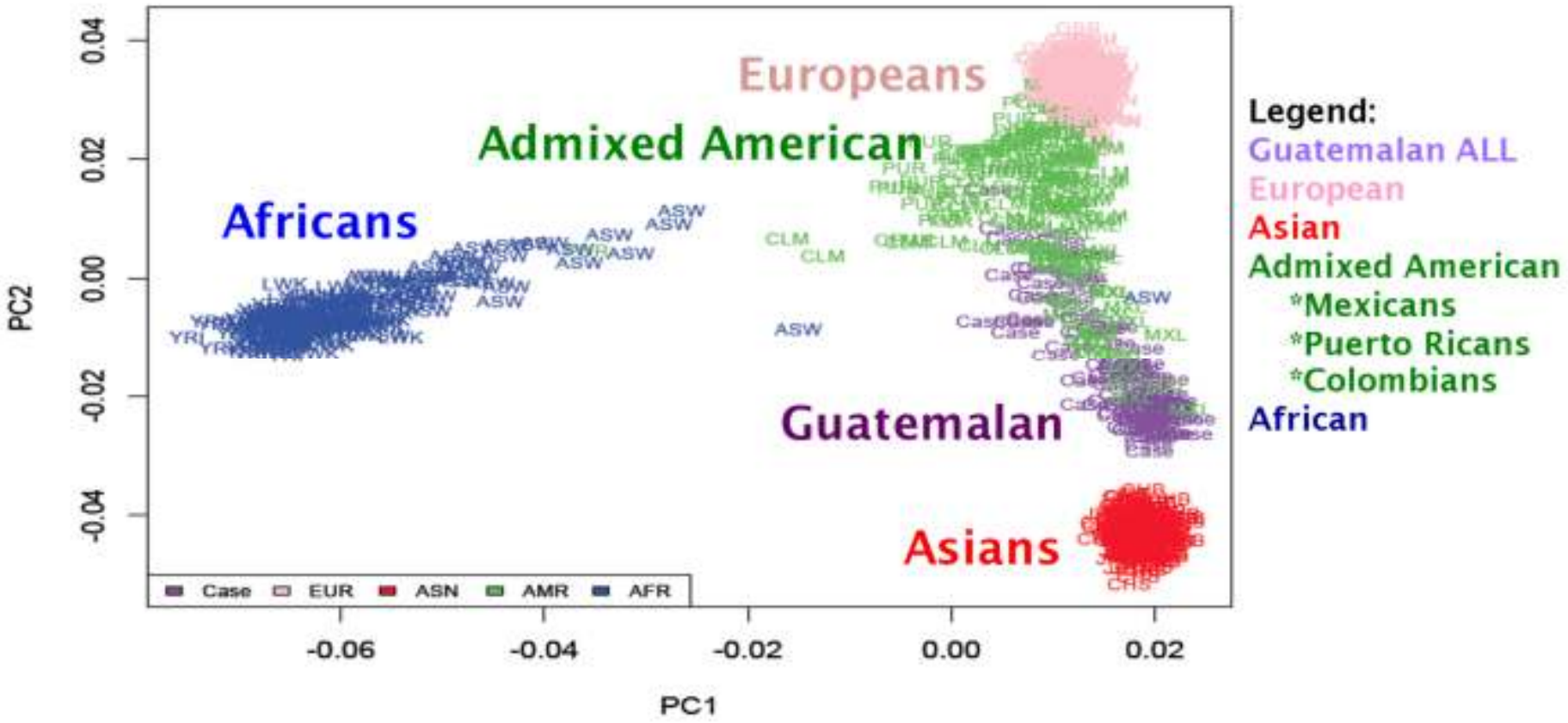
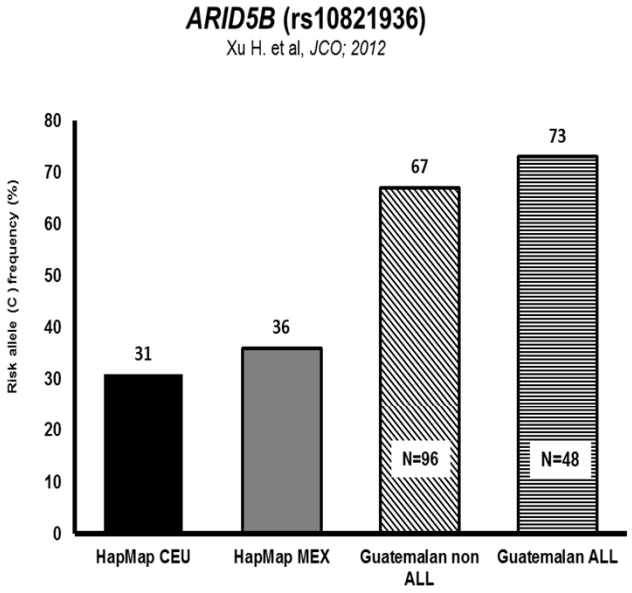
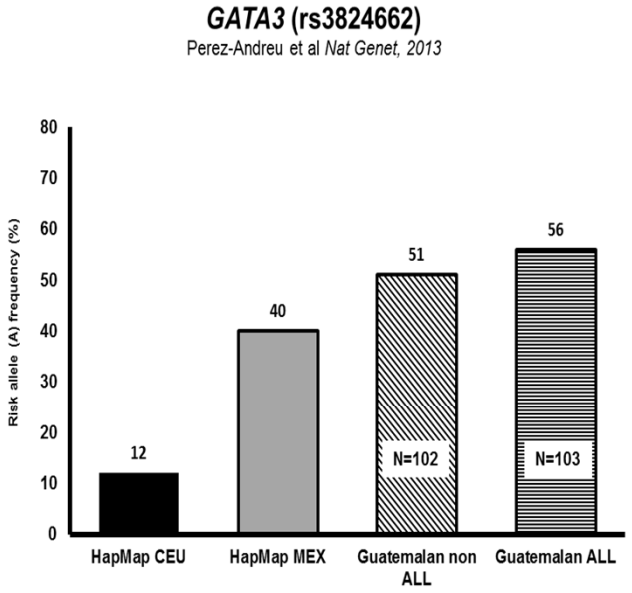
Uncovering population structure with ADMIXTURE

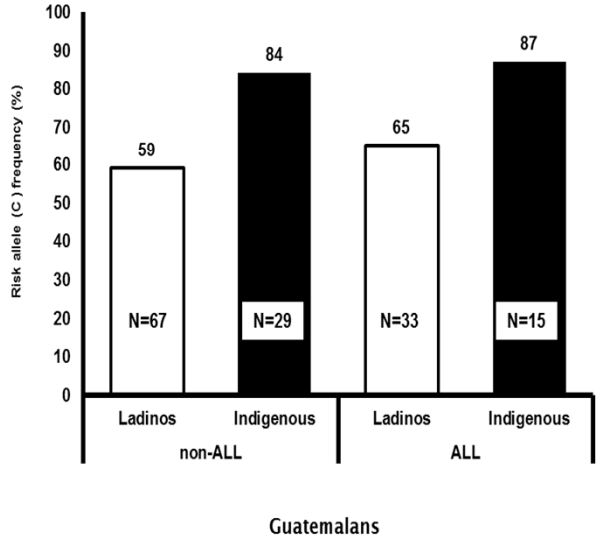


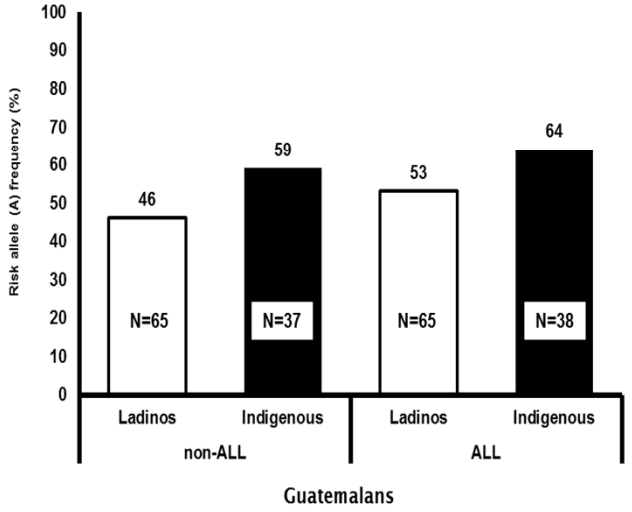
Uncovering population structure using Admixture. Using admixture as a software tool an estimation of individual ancestries was calculated by using 69,832 ancestry informative markers (Affymetrix 6.0 genotyping array) in 104 ALL cases from Guatemala and a multiethnic panel as a reference (http://www.1000genomes.org)

Inherited genetic variation in Native American individuals









Frequency description of ALL risk alleles for candidate SNPs at *ARID5B* and *GATA3* genes in Guatemalans individuals. The frequency of the ALL-related alleles at *ARID5B* (**Figure A**) and *GATA3* (**Figure B**) are shown in an ascending order for HapMap populations and Guatemalans individuals (non ALL and ALL cases). Risk allele frequency at *ARID5B* (**Figure C**) and *GATA3* (**Figure D**) SNPs are shown for Guatemalan individuals based on self-reported ethnicity (ladino *vs.* indigenous)

Conclusion

- **Guatemalan subjects** have exceptionally high level of **Native American ancestry (average at 82%)** compared to Mexicans (49%), Colombians (25%) or Puerto Ricans (13%).
- Admixture analyses indicate a close ancestral relationship between Guatemalans with the US Hispanics.
- **The frequency of inherited ALL susceptibility variants in *ARID5B* and *GATA3* are significantly over-represented in Guatemalans, indicating plausible association with Native American genetic ancestry**.

nature genetics

Inherited *GATA3* variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse

Virginia Perez-Andreu[1], Kathryn G Roberts[2], Richard C Harvey[3], Wenjian Yang[1], Cheng Cheng[4], Deqing Pei[4], Heng Xu[1], Julie Gastier-Foster[5,6], Shuyu E[1], Joshua Yew-Suang Lim[1,7], I-Ming Chen[3], Yiping Fan[8], Meenakshi Devidas[9], Michael J Borowitz[10], Colton Smith[1], Geoffrey Neale[11], Esteban G Burchard[12], Dara G Torgerson[12], Federico Antillon Klussmann[13], Cesar Rolando Najera Villagran[13], Naomi J Winick[14], Bruce M Camitta[15], Elizabeth Raetz[16], Brent Wood[17], Feng Yue[18], William L Carroll[16], Eric Larsen[19], W Paul Bowman[20], Mignon L Loh[21], Michael Dean[22], Deepa Bhojwani[23], Ching-Hon Pui[23], William E Evans[1], Mary V Relling[1], Stephen P Hunger[24], Cheryl L Willman[3], Charles G Mullighan[2] & Jun J Yang[1]

Recent genomic profiling of childhood acute lymphoblastic leukemia (ALL) identified a high-risk subtype with an expression signature resembling that of Philadelphia chromosome–positive ALL and poor prognosis (Ph-like ALL). However, the role of inherited genetic variation in Ph-like ALL pathogenesis remains unknown. In a genome-wide association study (GWAS) of 511 ALL cases and 6,661 non-ALL controls, we identified a susceptibility locus for Ph-like ALL (*GATA3*, rs3824662; $P = 2.17 \times 10^{-14}$, odds ratio (OR) = 3.85 for Ph-like ALL versus non-ALL; $P = 1.05 \times 10^{-8}$, OR = 3.25 for Ph-like ALL versus non-Ph-like ALL), with independent validation. The rs3824662 risk allele was associated with somatic lesions underlying Ph-like ALL (*CRLF2* rearrangement, *JAK* gene mutation and *IKZF1* deletion) and with variation in *GATA3* expression. Finally, genotype at the *GATA3* SNP was also associated with early treatment response and risk of ALL relapse. Our results provide insights into interactions between inherited and somatic variants and their role in ALL pathogenesis and prognosis.

approximately 20% of patients with high-risk features (for example, older age and higher leukocyte count at diagnosis, Philadelphia chromosome–positive (Ph+) ALL)[2–5].

Recent genomic profiling studies have shown the remarkable heterogeneity of childhood ALL, with more granular classification of molecular subtypes. Up to 15% of childhood B-lineage ALL cases exhibit a gene expression signature similar to that of Ph+ ALL[6–9]. Defined by this common expression profile, the 'Ph-like' ALL subtype has a range of structural genetic alterations in the tumor genome that activate lymphoid development, cytokine receptor and kinase signaling pathways. Ph-like ALL commonly harbors somatic *IKZF1* deletion or mutation[6,9]. Up to 50% of Ph-like ALL cases carry *CRLF2* rearrangements, with concurrent *JAK* gene mutations in approximately half of *CRLF2*-related cases[8,10]. Ph-like ALL cases without *CRLF2* alterations harbor a range of genomic lesions targeting cytokine receptors and tyrosine kinases[7]. Importantly, Ph-like ALL is associated with high risk of relapse[6,8,11].

GWAS efforts have identified germline SNPs in *ARID5B*, *IKZF1*, *CEBPE*, *PIP4K2A* and *CDKN2A-CDKN2B* that strongly influence sus-

nature genetics

NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity

Takaya Moriyama[1,2], Rina Nishii[1,3,22], Virginia Perez-Andreu[1,22], Wenjian Yang[1], Federico Antillon Klussmann[4,5], Xujie Zhao[1], Ting-Nien Lin[1], Keito Hoshitsuki[1,6], Jacob Nersting[7], Kentaro Kihira[2], Ute Hofmann[8,9], Yoshihiro Komada[2], Motohiro Kato[10], Robert McCorkle[1], Lie Li[1], Katsuyoshi Koh[11], Cesar Rolando Najera[4], Shirley Kow-Yin Kham[12], Tomoya Isobe[13], Zhiwei Chen[12], Edwynn Kean-Hui Chiew[12], Deepa Bhojwani[14], Cynthia Jeffries[15], Yan Lu[15], Matthias Schwab[8,9,16,17], Hiroto Inaba[18], Ching-Hon Pui[18], Mary V Relling[1], Atsushi Manabe[19], Hiroki Hori[2], Kjeld Schmiegelow[7,20], Allen E J Yeoh[12,21], William E Evans[1] & Jun J Yang[1]

Widely used as anticancer and immunosuppressive agents, thiopurines have narrow therapeutic indices owing to frequent toxicities, partly explained by *TPMT* genetic polymorphisms. Recent studies identified germline *NUDT15* variation as another critical determinant of thiopurine intolerance, but the underlying molecular mechanisms and the clinical implications of this pharmacogenetic association remain unknown. In 270 children enrolled in clinical trials for acute lymphoblastic leukemia in Guatemala, Singapore and Japan, we identified four *NUDT15* coding variants (p.Arg139Cys, p.Arg139His, p.Val18Ile and p.Val18_Val19insGlyVal) that resulted in 74.4–100% loss of nucleotide diphosphatase activity. Loss-of-function *NUDT15* diplotypes were consistently associated with thiopurine intolerance across the three cohorts ($P = 0.021$, 2.1×10^{-5} and 0.0054, respectively; meta-analysis $P = 4.45 \times 10^{-8}$, allelic effect size = −11.5). Mechanistically, NUDT15 inactivated thiopurine metabolites and decreased thiopurine cytotoxicity *in vitro*, and patients with defective *NUDT15* alleles showed excessive levels of thiopurine active metabolites and toxicity. Taken together, these results indicate that a comprehensive pharmacogenetic model integrating *NUDT15* variants may inform personalized thiopurine therapy.

Received 28 September 2015; accepted 15 January 2016; published online 15 February 2016; doi:10.1038/ng.3508

2. Políticas de Salud en Cáncer Pediátrico

- ¿Están los cuidados de cáncer pediátrico cubiertos en su país?
- ¿Existen datos/estimaciones del porcentaje de cobertura?
- ¿Cómo se financian los cuidados de cáncer pediátrico en su país?
- ¿Existe un acceso equitativo a los cuidados de cáncer pediátrico

Tasa por Región (por Millón de habitantes) Casos registrados, esperados y faltantes

REGION	Tasa por región	Casos registrados	Casos esperados	Casos faltantes
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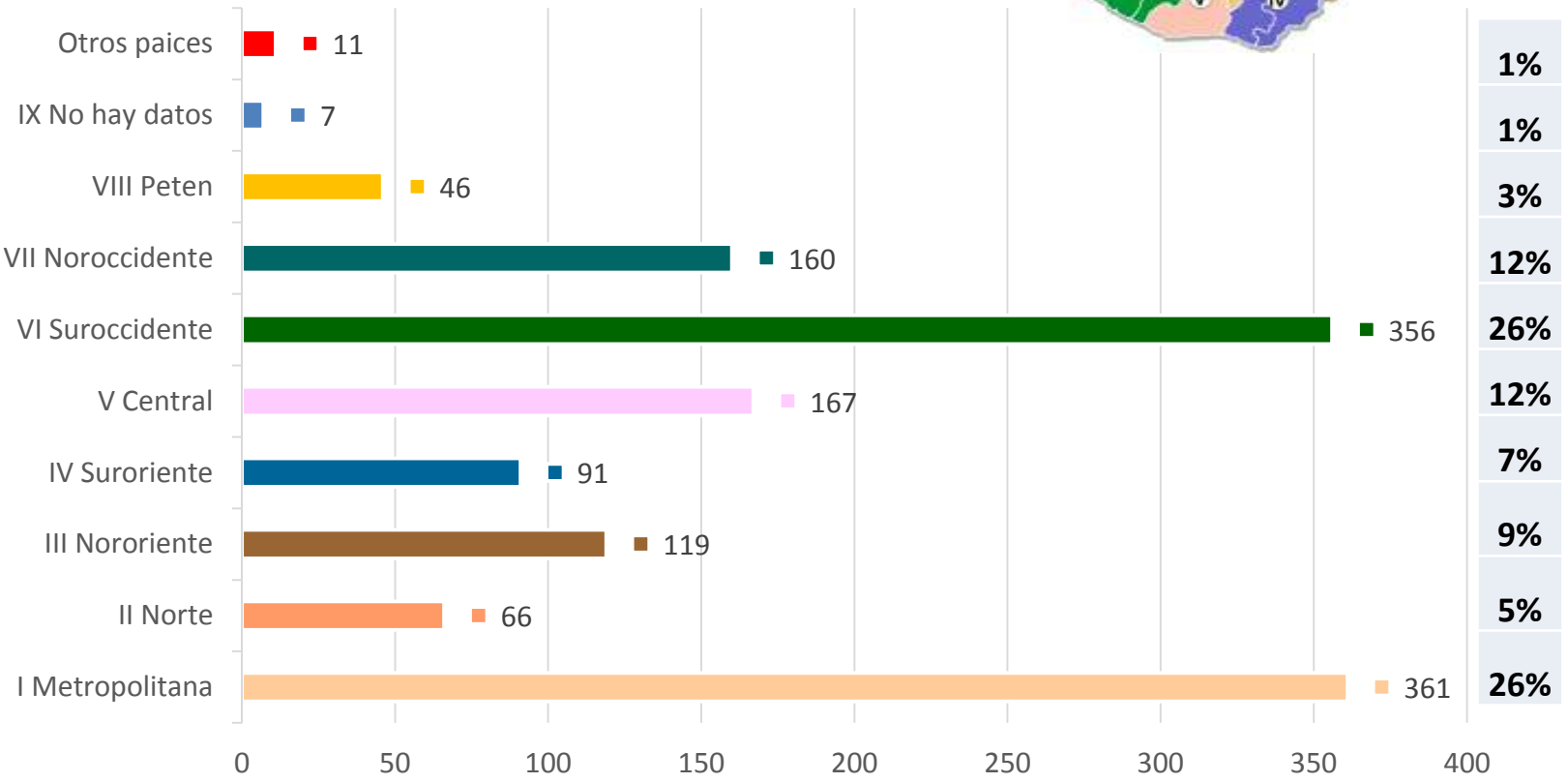
Suroccidente	73.2	119	194	-76
Noroccidente	50.6	53	127	-73
Petén	45.6	15	40	-25
Pais	72.0	455	769	-313

DISTRIBUCION POR AREA (No. 1383)



UNOP Budget

AYUVI

Q 80.8 MM

$10.63 MM

- Corporate Únete donors
- St. Jude Childrens Research Hospital (2%)
- Other institutions
- Padrinos (Godfather program)
- Events
- Proyects

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Q 120.8 MM

$ 15.89 MM

OPEX + CAPEX 2017

Ministerio de Salud Pública y Asistencia Social

Q 40.0 MM

$ 5.26

3. Sistema de Salud y Cuidados de Cáncer Pediátrico en Guatemala

- ¿Cómo es la calidad de los servicios de cáncer pediátrico? mejorable
- ¿Existe suficiente capacidad (equipamientos y recursos humanos) para facilitar la detección temprana y el tratamiento de cáncer pediátrico? En desarrollo
- ¿Está el personal de salud suficientemente capacitado? En el nivel primario y secundario no
- ¿Existen programas de capacitación para cuidados de cáncer pediátrico en su país? sí

Equipo Médico Multidisciplinar

- Hemato-Oncólogos pediatras
- Infectólogos pediatras
- Enfermeras Nosocomiales
- Radioterapia
- Farmacéuticos
- Laboratorio Clínico
- Radiología
- Intensivistas pediatras
- Anestesiólogos
- Cirujanos pediatras, ortopedas, otorrinos
- Pediatras
- Nutricionistas
- Medicina Integral (Paliativo, Psicología, T. Social, Child Life)
- Patólogos
- Enfermeras graduadas
- Auxiliares de enfermería
- Residentes y Fellows
- Otros especialistas en pediatría
- www.Cure4kids.org

José Ramírez, 12 años
Leucemia Linfoblástica

Hospicio, Hogar Estuardo Mimi

Clínica Satélite, Xela

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UFM
UNIVERSIDAD FRANCISCO MARROQUÍN
FACULTAD de MEDICINA

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Posgrado Hemato-Oncología Pediátrica

Cuidados Intensivos Pediátricos

Diplomado en Cuidados Paliativos

www.ufm.edu

Especialistas Egresados & formación

¡Se han graduado 22 especialistas!

23. Janine Alfaro	December 2017	Guatemala	3rd year Fellow	IOP	Started Jan 2015
24. Nidia López	July 1, 2018	Nicaragua	2nd year Fellow	IOP	Started July 2015
25.Sergio Quintanilla	July 1, 2018	Honduras	2nd year Fellow	IOP	Started July 2015
26. Tania Ardon	December 2018	El Salvador	2nd year Fellow	IOP	Started January 2016
27. Vivian Reyna	December 2018	Bolivia	2nd year Fellow	IOP	Started January 2016
28. Sharon Lewis	December 2018	Belice	NA	IOP	Started January 2016, left program October 2016.
29.Gerardo Castro		Honduras	1st year Fellow	IOP	Started January 2017
30. Mario A. Rodriguez		Guatemala	1st year Fellow	IOP	Started January 2017
31.Andrea Cordón		Guatemala	1st year Fellow	IOP	Started January 2017
32.Karla Cruz		Bolivia	1st year Fellow	IOP	Started January 2017

4. Carencias, Retos, y Oportunidades para la Mejora del cuidado de Cáncer Pediátrico en Guatemala

Fortalezas

- Iniciativa público privada exitosa
- Apoyo St Jude Global
- Liderazgo local fuerte
- Coordinación regional AHOPCA
- Programas de formación con aval Universitario
- Investigación

Debilidades

- Las necesidades son mayores que los recursos disponibles
- Escasez de especialistas y personal de salud
- Infraestructura saturado (% ocupación 95%+)
- Debilidad del Ministerio de Salud
- Corrupción en el ambito público

Oportunidades

- Promover el diagnóstico temprano
- Mejorar las capacidades de diagnóstico (MDR, B. Molecular, Patología revisión central, otras nuevas tecnologías)
- Fortalezer la docenciay la investigación
- Ampliar infraestructura
- Mejorar la recaudación local e internacional

Amenazas

- Infecciones por bacterias multiresitentes en los niños con cáncer
- Competencia de otras prioridades de salud
- Instituciones débiles

Metastáticos por país (Estadio St Jude)

(No=68/396)

País	total	III*	IV*	%
Guatemala	**186**	**39**	**13**	**27.9%**
El Salvador	50	3	0	6%
Honduras	60	6	2	13%
Nicaragua	57	3	1	7%
Costa Rica	**43**	**1**	**0**	**2.3%**
Total	396	52	16	17%

65% indigenas
33% mestizos

*** Todos los estadios III y IV fallecen!!!**

Diagnóstico temprano del cáncer en la niñez

Organización Panamericana de la Salud

Organización Mundial de la Salud

Américas

aiepi

Organización Panamericana de la Salud

Organización Mundial de la Salud

Américas

aiepi

9 789275 316401

“Design and implementation of an integral instrument with cultural belonging, to increment early cancer detection in patients under 18 years old, in the first level of health care network of the Ministry of Public Health and Social Assistence of Guatemala”.

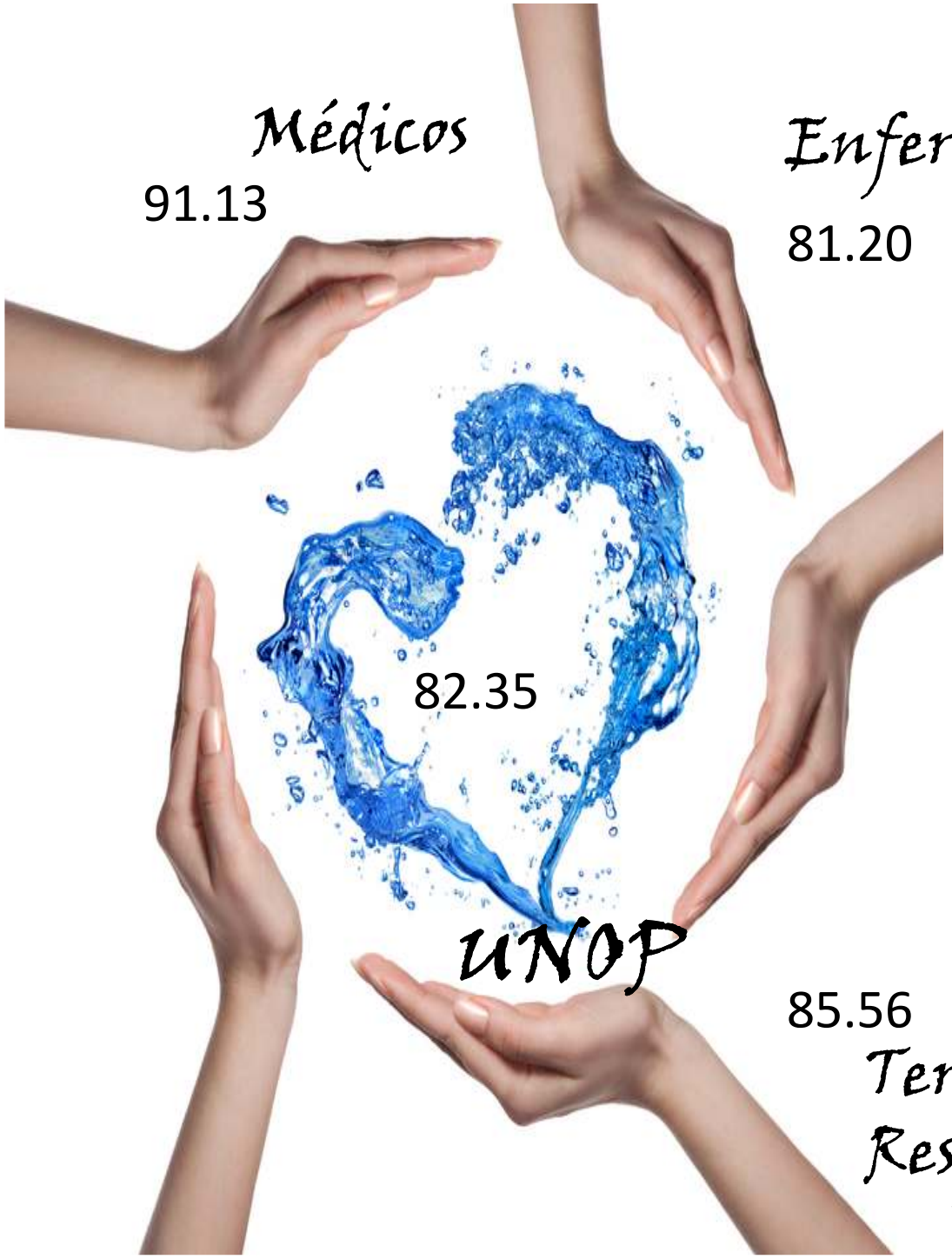
Lavado de manos

Médicos

91.13

Enfermería

81.20



82.35

UNOP

85.56

Terapia Respiratoria

5. Actores Clave para los Cuidados de Cáncer Pediátrico en Guatemala

- Sobrevivientes cáncer
- La Comunidad
- AYUVI-UNOP-MSPAS
- St Jude Children´s Research Hospital/ALSAC; St Jude Global
- Universidad Francisco Marroquín
- AHOPCA
- MISPHO
- My Child Matters
- Boston Children´s/Dana Farber

6. Apoyo Necesario para Establecer un Programa de Cáncer Pediátrico

- ¿Qué tipo de apoyo necesita su país para establecer programas de cáncer pediátrico? Para el mantenimiento y crecimiento del programa ,se requiere aumentar los recursos económicos de las mismas fuentes u otras fuentes de recursos
- Resuma cuáles son los resultados que espera de esta reunión o del trabajo de este grupo?coordinación de esfuerzos internacionalmente, conocer nuevas fuentes de recursos.

7. Conclusiones

- Establecer un programa de cáncer pediátrico en un país LMIC es posible.
- Un modelo público-privado es una solución en paises LMIC
- La colaboración internacional es impresindible

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Global Pediatric Oncology: Lessons From Partnerships Between High-Income Countries and Low- to Mid-Income Countries

Raul C. Ribeiro, Federico Antillon, Francisco Pedrosa, and Ching-Hon Pui

Raul C. Ribeiro and Ching-Hon Pui, St Jude Children's Research Hospital, Memphis, TN; Federico Antillon, Unidad Nacional de Oncologia Pediatrica and Universidad Francisco Marroquin, Guatemala City, Guatemala; and Francisco Pedrosa, Instituto de Medicina Integral Fernando Figueira, Recife, Brazil.

Published online ahead of print at

ABSTRACT

Partnerships between medical institutions in high-income countries (HICs) and low- to mid-income countries (LMICs) have succeeded in initiating and expanding pediatric cancer control efforts. The long-term goal is consistently a sustainable national pediatric cancer program. Here, we review the elements required for successful implementation, development, and long-term sustainability of pediatric cancer programs in LMICs that first arise as partnerships with institutions in HICs. Although plans must be adapted to each country's resources, certain components are unfailingly necessary. First, an essential step is provision of treatment regardless of ability to pay. Second,

Gracias!!!